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Review Article

The effect of pain on the neuronal activity in the hypothalamic arcuate nucleus and its consequences on the reproductive axis

Khadijeh Haghighat, Fariba Mahmoudi*

Department of Biology, Faculty of Science, University of Mohaghegh Ardabili, Ardabil, Iran

ABSTRACT

Pain, an unpleasant feeling resulting from physical or psychological damage, manifests in various diseases such as migraine, fibromyalgia, rheumatoid arthritis, back pain, and neuropathy, disrupting the physiology of the body system. Prolonged pain can detrimentally affect other body tissues, leading to disorders by interfering with hormone secretion. Several studies show that pain can damage the reproductive process. Within the hypothalamus, a population of kisspeptin, neurokinin B, and dynorphin (KNDy) neurons plays an important role in regulating the reproductive axis. This study aims to investigate the effect of pain on hypothalamic neuron activity and its subsequent implications on the reproductive pathway.

Keywords:
Pain
Reproduction
Hypothalamus
Hypothalamic Arcuate nucleus

Introduction

Reproductive function is under the control of the central and peripheral system. Hypothalamic neuropeptides, pituitary gonadotropins, and peripheral sex hormones are critical factors in regulating the reproductive axis. The coordinated cooperation of the hypothalamic-pituitary-gonadal (HPG) axis is necessary for follicular development and ovulation. Gonadotropin-releasing neurons (GnRH) are located in the hypothalamus. The pulsatile secretion of GnRH is important for proper reproductive function. Intracerebral (neuropeptides and neurotransmitters) and environmental (ovarian estrogen by negative feedback) factors affect hypothalamic neuron activity. Therefore, any disruption in these neurons' function can adversely affect the reproductive process (Nagae et al., 2021).

Evidence suggests that the hypothalamic ARC nucleus contains a population of kisspeptin, neurokinin B, and dynorphin A neurons, also known as KNDy neurons. These neurons play a key role in GnRH pulse secretion in female mammals, rodents, and ruminants. KNDy neurons seem to act as mediators for the action of estrogen on GnRH (Mittelman-Smith et al., 2012). Kisspeptin is expressed by kiss1 gene, norkinin B by Tac3 gene, and dynorphin by Pdyn gene. It has been observed that mutations in the kisspeptin receptor gene (GPR54) and neurokinin receptor 3 (NKR3) lead to hypogonadism and hypogonadotropic respectively. GnRH neurons

* Corresponding author: Fariba Mahmoudi, f.mahmoudi@uma.ac.ir
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receive most synaptic input (approximately 60%) from KNDy neurons. Simultaneous cooperation of all three neuropeptides kisspeptin-neurokinin B-dynorphin is important (Nagae et al., 2021; Aerts et al., 2021). Kisspeptin, a 54-amino acid neuropeptide, orchestrates the pulsatile secretion of gonadotropins. Kisspeptin receptors on GnRH neurons, expressed by the kissR1 gene, stimulate LH secration across species. Neurokinin B acts as an initiation signal in the KNDy network, while dynorphin plays a role in stopping GnRH pulses (Lehman et al., 2020). Therefore, neurons expressing kisspeptin or neurokinin B peptides play an important role in fertility regulation (Moore et al., 2018). Evidence suggests that KNDy neurons drive GnRH pulses in the hypothalamus (figure1). Even the regeneration of at least 20% of KNDy neurons suffices to generate ovarian follicles through the generation of GnRH/gonadotropin pulses (Nagae et al., 2021). Therefore, any disruption in the KNDy network can impair proper reproductive function.

Pain, an unpleasant experience, involves a complex physiological process triggered by physical stimuli or emotional processes. Following a noxious stimulus, a sequence of electrical and chemical events occurs, ultimately transmitting pain signals via sensory fibers to higher centers. These signals are received and interpreted by different areas of the central nervous system, such as the thalamus and cerebral cortex (Hudspith, 2016). The feeling of pain can disrupt normal physiological processes within the body. In the central nervous system, pain can disrupt the release of neurotransmitters, which can contribute to certain disorders. Evidence suggests that the secretion of steroid hormones is impaired in people suffering from pain. Neurons located in the hypothalamus, such as GnRH neurons, control steroid hormone secretion. Therefore, pain can perturb the reproductive pathway by affecting KNDy neurons that regulate the activity of GnRH neurons (Multon et al., 2005).

Pain and Reproduction axis

Pain, an unpleasant feeling experienced by individuals, can significantly impact their lives, potentially leading to disability and crises. When pain occurs for any reason, it is transmitted via nerve fibers to the spinal cord, then to the thalamus, and subsequently percieved by different brain areas such as the amygdala and frontal cortex. Finally, the brain processes and responds to these signals. Due to its influence on several central nervous system (CNS) networks, pain can disrupt various brain signals, potentially causing disorders (Yang and Chang, 2019). The hypothalamic ARC nucleus contains KNDy neurons, pivotal in modulating pain perception. Also, ARC nucleus has neurons releasing GnRH, kisspeptin,

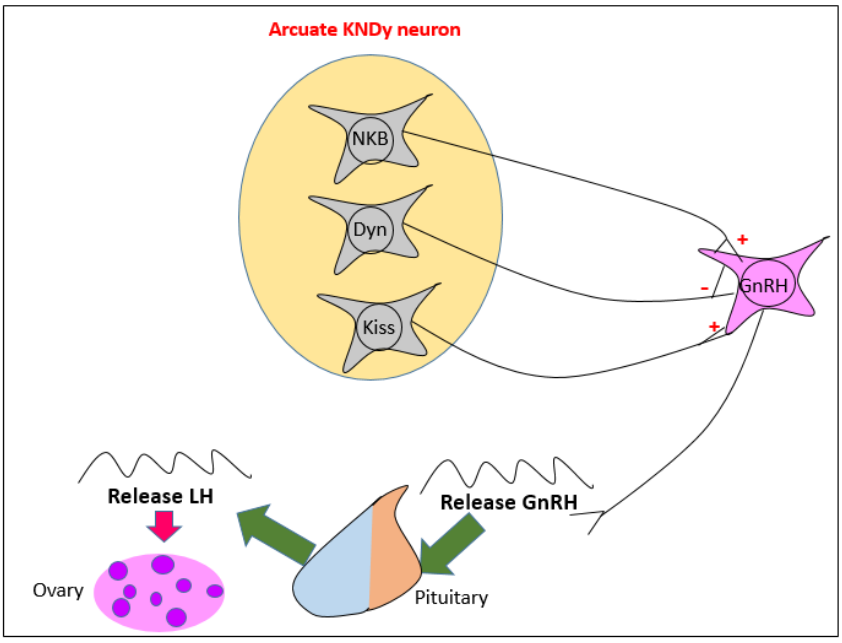

FIGURE 1. The role of KNDy neurons in the regulation of GnRH secretion.

and neurokinin B, crucial for the reproductive process. Therefore, any pain-inducing stimulus affecting the ARC nucleus may disrupt the reproductive axis. Diseases such as neuropathy, migraine, fibromyalgia, arthritis, and skeletal diseases are known to induce pain. Studies indicate their potential to impact reproductive hormones, potentially impairing fertility (Ma et al, 2019).

Musculoskeletal Pain and Reproduction axis

Musculoskeletal pain is one of the causes of disability in individual. According to the report of the World Health Organization (WHO), almost 30% of the world's population suffers from musculoskeletal chronic pain (El-Tallawy et al., 2021). Musculoskeletal pain affects bones, muscles, ligaments, and nerves. Chronic pain reduces a person's quality of life and impose an enormous economic cost on the healthcare system. In people suffering from musculoskeletal pain, physical activity is usually reduced due to pain. Decreased physical activity is also related to various diseases such as diabetes and obesity (Tüzün, 2007). Studies have shown a close relationship between diabetes and infertility. Diabetes Mellitus, by increasing oxidative stress, reduces sperm life and damages sperm DNA. In addition, there are changes in the levels of LH and FSH in diabetic patients (Condorelli et al., 2018). A study on diabetic model rats shows that diabetes is associated with suppressing KNDy neurons. Therefore, musculoskeletal pain can lead diseases such as obesity and diabetes by reducing activity in a person. Also, diabetes disrupts the activity of neurons in the ARC nucleus and causes disturbances in the menstrual cycle and fertility (Enomoto et al., 2022). Most people suffering from chronic musculoskeletal pain use strong painkillers. It is reported that long-term administration of opioid drugs causes reproductive dysfunction (hypogonadism) in men (Richardson, 2019). Another study has shown that the widespread use of opioid drugs in reproductive age can negatively affect fertility. Opioid analgesics can affect reproduction and reproductive outcomes through various mechanisms. Opioids have a significant effect on endocrine secretion, especially the release of gonadotropins and estrogen. Opiate receptors are present on ovaries, endometrium, testes, and sperm in humans. Opioid drugs cross the placenta and can disrupt normal endocrine regulation in both men and women. Also, hypogonadism and amenorrhea occur with long-term use of opioid drugs (Flannagan et al., 2020). The increasing prevalence of pain and attempts to treat chronic pain are probably the reasons for the long-term use of opioid drugs. Therefore, the use of these drugs exposes women to risks related to endocrine glands, reduced fertility, and cardiovascular risks (Darnall et al., 2012).

Fibromyalgia and Reproduction axis

Fibromyalgia is a common chronic musculoskeletal pain syndrome with a distinct clinical phenotype. The etiology of fibromyalgia is unclear, and there are no biomarkers to diagnose this type of pain. Individuals with fibromyalgia typically experience long-term pain, characterized by touch and felt more in the axial and proximal areas of the body. Notably, there are no anatomical lesions in people with fibromyalgia. This type of pain may be related to sensory inputs to the brain and is often associated with fatigue, depression, and sleep disturbance. Various treatment strategies, including drug and non-drug therapy, are used to manage fibromyalgia. Findings suggest that many brain networks are disturbed in fibromyalgia, with higher levels of glutamate in the posterior insular region observed in individuals with fibromyalgia (Littlejohn and Guymer, 2018; Shin et al., 2020). Also, levels of other neurotransmitters such as substance P and N-methyl aspartate (NMDA) change in fibromyalgia. A cerebrospinal fluid (CSF) proteomics study reveals that proteins regulating lipoprotein lipase activity, energy metabolism, and certain peptides are involved in the development of fibromyalgia. Other evidence shows that disruption in the serotogenic system is also a factor in fibromyalgia syndrome, as the level of tryptophan, a precursor of serotonin or 5-Hydroxy tryptamine(5-HT), decreases in fibromyalgia. 5-HT helps reduce pain and promote restful sleep, linking the reduction of 5-HT to insomnia and pain in individuals with fibromyalgia. In addition, people with fibromyalgia may experience digestive, memory, and reproductive disorders (Koné et al., 2021; Russell, 1998).

Several studies have reported a link between fibromyalgia and infertility. Pain can affect the reproductive process through different mechanisms. In fibromyalgia, the activity of the hypothalamus-pituitary-adrenal (HPA) axis is disturbed. Hyperactivity of the HPA axis, by sending a message to Corticotropin-Releasing Hormone (CRH), stimulates the release of Adrenocorticotropic Hormone (ACTH), causing excessive secretion of

cortisol from the adrenal gland. CRH, synthesized in the CNS in the ARC, has receptor present in the placenta, ovary, and endometrium, indicating the important role of CRH in reproductive process. Changes in CRH secretion reported in fibromyalgia patients could affect the function of other hormonal axes. Moreover, there is a close relationship between the HPA axis and the hypothalamic-pituitary-gonadal (HPG) axis. The HPG axis regulates the reproductive process through GnRH, stimulating the secretion of FSH and LH and sex hormones. Increased CRH secretion, due to hyperactivity of the HPA axis, inhibits the release of GnRH, potentially disrupting the ovulation process by affecting the ovaries (Koné et al., 2021; Tanriverdi et al., 2007).

Pro-inflammatory cytokines may play a role in the development of fibromyalgia. Several studies show that pro-inflammatory cytokines, such as IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), are increased in the serum of people with fibromyalgia. It is reported that increased levels of pro-inflammatory cytokines in the brain and spinal cord trigger pain (Coskun Benlidayi, 2019). Kisspeptin, a 54 amino acid neuropeptide synthesized by neurons in the hypothalamus, plays an important role in regulating GnRH function. Kisspeptin receptors are expressed in the ovary, testicle, and pancreas. Suppression of kisspeptin in the hypothalamic ARC is associated with reduced GnRH release. Another study has shown that increased pro-inflammatory factors decrease kisspeptin neuron activity, leading to a decrease in LH levels (Harter et al., 2018). Dynorphin, a neuropeptide in the brain released by neurons in the ARC of the hypothalamus, together with kisspeptin and neurokinin B, is essential in the regulation of GnRH secretion in mammalian reproduction. Dynorphin inhibits GnRH secretion by binding to opioid receptors on the surface of gonadotropin-releasing neurons (Moore et al., 2018; Ruiz-Pino et al., 2015). Studies show that a decrease in dynorphin is directly related to pain. Therefore, in people with fibromyalgia, the expression level of dynorphin decreases, negative affecting the reproductive process.

Migraine and Reproduction axis

Migraine is a common headache that affects 15% of the world's population, lasting typically from 4 to 72 hours and disrupting routine activities. It is associated with nervous, digestive, nausea, and vomiting symptoms, categorizing it as a neurological disorder. Migraine pain, usually one-sided, spreads to different areas of the brain, and sufferers are often sensitive to light, seeking relief in darkness. The prevalence of migraine varies with age and sex, being more common in women than in men. The pathophysiology of migraine is intricate, involving structural and functional changes in the brain. Neuroimaging studies indicate depolarization in the cerebral cortex for about one-third of those experiencing migraines. Also, migraine can affect the morphology of the brain stem, cerebellum, and neural networks. The pain is likely caused by nociceptive fibers transmitting signals from intracranial and extracranial blood vessels and other cranial structures. During migraine attacks, there may be peripheral and central sensitization of pain pathways (Aykal et al., 2022; Ashina et al., 2021).

Several neurotransmitters and neural pathways contribute to migraine's pathophysiology, with the hypothalamus playing a significant role. The hypothalamus, connected with brain regions associated with pain processing and modulation, is implicated in the initiation of migraine attacks. Studies indicate its wide connection with some areas of the CNS, such as the brain stem, locus coeruleus, and the median raphe nucleus (Alstadhaug, 2009). Mechanisms of hypothalamus action on nociceptors are not well known. Various factors can cause hypothalamus disorder and migraine attacks. Stress, a potential trigger for migraine attacks, involves the dynorphin/kappa receptor (KOR) in the ARC and increases circulating prolactin, heightening pain receptor sensitivity in women (Watanabe et al., 2022). Also, studies show that the neurons in the hypothalamus can receive pain signals from the trigeminal nerve of the spinal cord, influencing hypothalamic function and endocrine activity, including hormone secretion, especially reproductive hormones (Martins-Oliveira et al., 2017). Gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, is distributed widely in the brain and plays a role in migraine. GABA's regulatory effect on cortical function, influencing NMDA receptor activity, is implicated in pain modulation. An imbalance between excitatory and inhibitory signals in the cerebral cortex is hypothesized to lead to migraine headaches. GABA's involvement in the excitatory-inhibitory regulation of the cerebral cortex may be significant in inducing migraines, and an increase in GABA metabolism may act as a compensatory process to limit migraine attacks (D'Andrea et al., 2001; Aguila et al., 2016). Additionally, GABA has been

Table1: The effect of pain on reproductive performance

Musculoskeletal Pain	- Suppressing the activity of KNDy neurons - The development of diabetes due to limitations in physical activity (Related to gonadotropins secretion disorder) - Disturbance in the secretion of LH and FSH hormones - Disruption of the reproductive axis by taking opioids for pain relief
Fibromyalgia	- Decreased 5-HT in fibromyalgia - Disturbance in the HPA axis and its effect on the secretion of GnRH in fibromyalgia -Stimulation of pain by increasing pro-inflammatory factors IL6, IL1, TNFa - Reducing the secretion of gonadotropins by reducing kisspeptin due to the increase of pro-inflammatory factors in fibromyalgia. - Decreased activity of GnRH neurons due to decreased expression of dynorphin in fibromyalgia
Migraine	- Decreased GnRH secretion with increased GABA in migraine attacks - Decreased activity of KNDy neurons by increasing GABA in migraine attacks
Neuropathic Pain	- Decreased activity of KNDy neurons in neuropathic pain - Inhibition of GnRH secretion by dopaminergic neuron activity in neuropathic pain - Inhibition of GnRH secretion through 5HT-A1 receptors

observed to have an inhibitory effect on GnRH biosynthesis at the hypothalamus level. The increased activity of the GABAergic system during migraine attacks may affect the activity of neurons in the hypothalamus, disrupting the secretion of sexual gonadotropins and influencing the reproductive process (Ciechanowska et al., 2019; Kanasaki et al., 2017).

Neuropathic Pain and Reproduction axis

Neuropathic pain, stemming from damage to the peripheral and central nervous system, results in abnormal processing of sensory fibers. Unlike pathophysiological pain, neuropathic pain persists chronically and does not subside over time with the cessation of noxious stimuli. This common chronic disorder significantly impacts a person's quality of life and is often accompanied by symptoms such as tingling and burning (Finnerup et al., 2021). Chemicals, including noradrenaline, bradykinin, histamine, prostaglandins, potassium, and cytokines, are released from damaged and inflammatory cells when the peripheral nervous system is compromised. These mediators induce changes in ion channels, especially sodium ion channels, stimulating nociceptors and lowering the pain threshold. In the case of neuropathic pain, central mechanisms also play an important role. It is thought that the long-term release of tachykinins, including neuropeptide substance P and neurokinin A, and the neurotransmitters glutamate, calcitonin gene-related peptide causes hyperexcitability of pain neurons in the CNS (Pasero, 2004; Abd-Elsayed et al., 2019).

Neuroimaging studies have demonstrated structural changes in different brain areas during neuropathic pain, particularly in the neuromatrix and cerebral cortex. In addition, studies show that the lateral hypothalamus (LH) plays a role in pain modulation. The hypothalamus can be involved in the modulation of pain through various mediating pathways. In the brain, a group of dopaminergic and serotonergic cells is distributed, which play a role in pain modulation. Dopaminergic cells called A11 are located in the hypothalamus, which helps control pain. Dopamine through D2/D3 receptors and 5-HT through 5-HT1A and 5-HT2A receptors suppress pain (Salehi et al., 2020; Martikainen et al., 2018). Also, changes in the activity of dopaminergic and serotonergic cells can disturb other neurons in the hypothalamus, such as GnRH and KNDy neurons. Studies reveal that dopamine inhibits GnRH secretion through D2 receptors in the ARC, suppressing the activity of kisspeptin neurons (Goodman et al., 2012). Furthermore, serotonergic neurons are directly connected to hypothalamic GnRH neurons. Evidence suggests that 5-HT has both inhibitory and stimulatory effects on GnRH neurons, inhibiting them through the 5HT-A1 receptor. Therefore, the mechanism through which pain adversely affects the activity of hypothalamic neurons likely involves intermediary pathways, ultimately influencing the reproduc-

tive axis by altering the function of these neurons (Saedi et al., 2018).

Conclusion

Reproductive function is controlled by the HPG axis. A population of GnRH and KNDy neurons are distributed in the hypothalamic ARC, which plays an important role in reproductive axis activity. GnRH release is under the control of KNDy neurons located in the hypothalamus. Also, different brain regions such as insula, cerebral cortex, thalamus, and amygdala are involved in modulating pain and are interconnected with the hypothalamus. Chronic pain has the potential to disrupt the reproductive axis by changing the activity of hypothalamic neurons. Consequently, experiencing prolonged pain may lead to disturbances in the pain-modulating areas of the CNS, impacting the proper functioning of other brain centers. Addressing the source of chronic pain and implementing appropriate treatment strategies can be crucial in resolving fertility disorders.

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Conflict of interest

Authors declare no conflict of interest.

Ethics approval

This article is a review and has no code of ethics.

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