The Two “eyes” of Hypogonadism:

The influence of Ibuprofen and Inflammation on Testosterone Production

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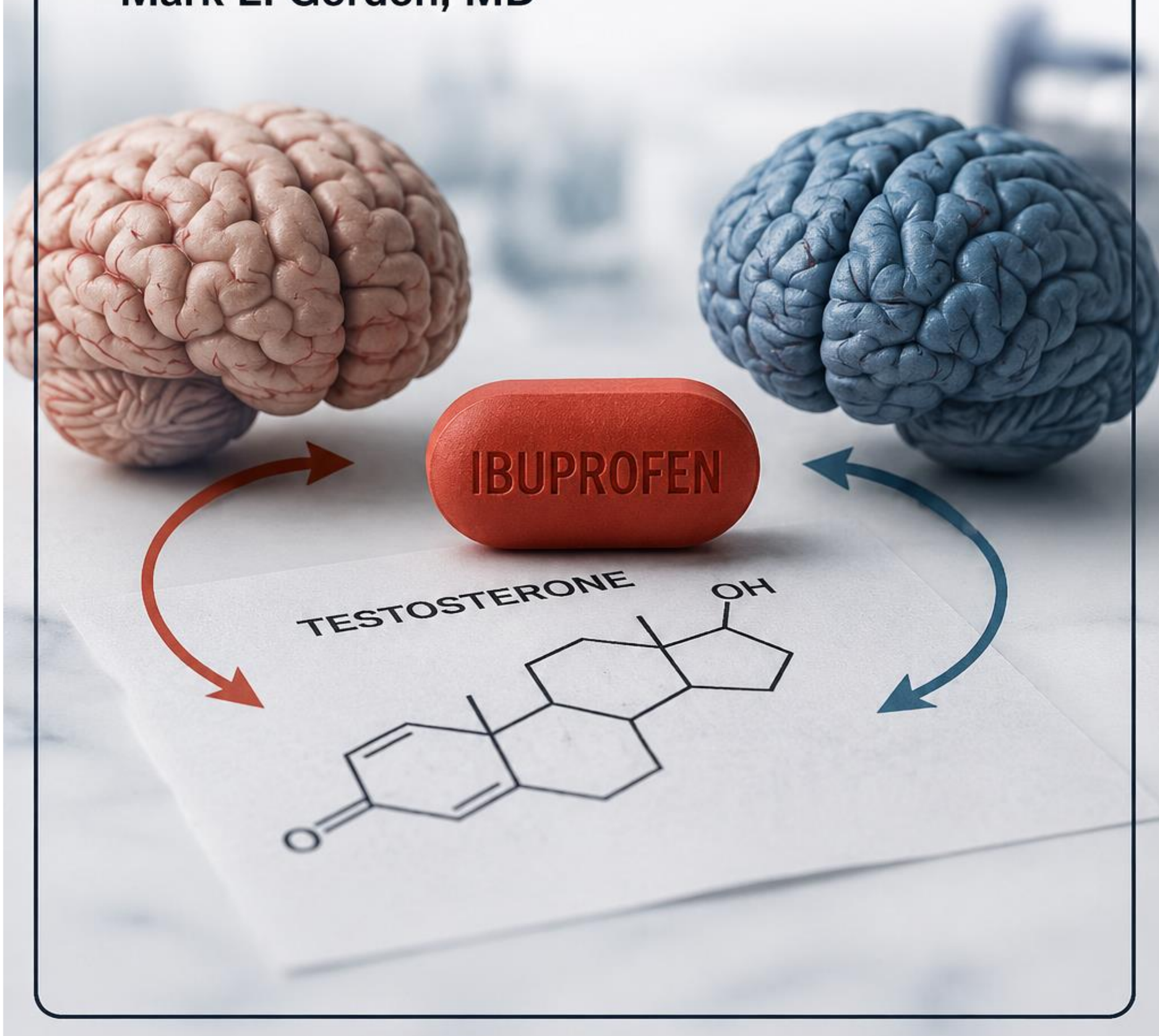

The Two "eyes" of Hypogonadism: The influence of **I**buprofen and **I**nflammation on Testosterone Production.

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Forward

A growing concern about the expansive number of special force operators developing testosterone deficiency has created an urgency to perform laboratory testing and to treat with hormone replacement therapies while failing to consider and assess causation. Our military, as well as elite athletes, are exposed to traumas that provoke an inflammatory response that is frequently addressed by the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. In 2017 researchers found that NSAIDs have a insidious effect on altering gonadal response to luteinizing hormone (LH) causing a reduction of steroidal hormone production. Adding insult to injury, the neuroinflammation precipitated by trauma causes neuroendocrine disruption that damages the hypothalamic regulatory control over the anterior pituitary gland leading to another avenue for the loss of testosterone production. In this paper, I will unfold the science relating to how to recognize and then fix the impact of neuroinflammation and NSAIDs on testosterone production. Only after this approach fails should low-dose testosterone therapy be considered.

Quick Read

This paper discusses how both inflammation and commonly used painkillers, such as ibuprofen, can interfere with the body's ability to produce and regulate hormones, particularly testosterone. While these medications are widely used to reduce pain and inflammation, they may also influence key processes in the body, leading to potential long-term hormonal imbalances.

Inflammation itself plays a significant role in disrupting hormone regulation. When the body experiences chronic inflammation, it can impair the function of the hypothalamus and pituitary gland, which are responsible for controlling hormone production. Inflammatory molecules can interfere with the release of gonadotropin releasing hormone (GnRH), the hormone that signals the production of testosterone, leading to lower levels over time. This natural response to prolonged inflammation can contribute to fatigue, reduced muscle mass, mood disorders, and other health issues associated with low testosterone.

Ibuprofen and other NSAIDs, while designed to reduce inflammation, can further disrupt this hormonal balance. These medications inhibit the production of prostaglandins, which are necessary for the normal function of the hypothalamus and pituitary gland. By reducing prostaglandin levels, NSAIDs may impair the release of GnRH, thereby suppressing testosterone production. Additionally, ibuprofen directly affects the function of the Leydig cells in the testes, which are responsible for testosterone synthesis.

Furthermore, other common painkillers, such as aspirin, naproxen, and diclofenac, have similar effects on hormone production, though they work in slightly different ways. Some interfere with brain signals, while others directly lower testosterone or estrogen levels. (See **Addendum A** for listing of NSAIDs)

Since both chronic inflammation and NSAID use can affect hormone balance, it is important to consider their combined impact on long-term health. While inflammation can suppress hormone production, excessive reliance on painkillers may also contribute to hormonal imbalances. A more comprehensive approach that addresses underlying inflammation through lifestyle, diet, and targeted medical interventions may be a more effective strategy for maintaining and reestablishing hormonal health.

Abstract

Ibuprofen, as well as other nonsteroidal anti-inflammatory drugs (NSAIDs), have been increasingly recognized as endocrine-disrupting chemicals (EDCs) with profound implication for male and female reproductive health. Chronic ibuprofen exposure disrupts key steroidogenic pathways, leading to a functional hypogonadal state characterized by suppressed testosterone production. This suppression is mediated through direct inhibition of Leydig and Thecal cell functions, interference with transcription factors essential for steroidogenesis, and disruption of endocrine feedback mechanisms.

Beyond its direct gonadal effects, ibuprofen exerts significant neuroendocrine influence by modulating neuroinflammation and glial function, particularly astrocytes, which play a crucial role in maintaining central hormonal homeostasis. As demonstrated by Sharif et al. (2013), astrocytes and tanycytes actively regulate gonadotropin-releasing hormone (GnRH) neuronal activity through the secretion of prostaglandin E2 (PGE2), a key gliotransmitter that facilitates GnRH release from the hypothalamus. PGE2-mediated activation of GnRH neurons is essential for maintaining pulsatile luteinizing hormone (LH) secretion, which in turn stimulates testosterone biosynthesis. However, **by dampening neuroinflammatory pathways**, ibuprofen disrupts astrocytic PGE2 production, leading to impaired GnRH pulsatility, reduced LH release, and subsequent testosterone deficiency.

Moreover, this paper explores the broader implications of ibuprofen-induced endocrine disruption, including its potential transgenerational effects and long-term consequences for reproductive and metabolic health. Given the widespread use of NSAIDs and their accessibility as over-the-counter medications, understanding their impact on the neuroimmune-endocrine axis is critical. By elucidating the complex interplay between neuroinflammation, glial function, and endocrine regulation, this paper will provide a comprehensive perspective on how NSAID exposure contributes to endocrine dysfunction and reproductive decline.

[**Keywords**: non-steroidal anti-inflammatory drugs, hypogonadism, PGE2, neuroinflammation, translational repression]

Introduction

Ibuprofen, a widely used nonsteroidal anti-inflammatory drug, is commonly employed for its analgesic and anti-inflammatory properties. However, emerging evidence suggests that chronic exposure to ibuprofen can result in significant endocrine disruption, particularly affecting reproductive health. Studies have demonstrated that ibuprofen downregulates key genes essential for testosterone biosynthesis by suppressing transcriptional regulators involved in steroidogenesis, ultimately leading to a functional **hypogonadal state** (Kristensen et al., 2018). This suppression is largely mediated through the inhibition of luteinizing hormone (LH) secretion and impairment of Leydig cell function, resulting in diminished testosterone production (Bastien et al., 2018).

Beyond its direct gonadal effects, ibuprofen has been shown to exert profound neuroendocrine disruptions by modulating neuroinflammation and astrocyte function. Research indicates that glial cells, particularly astrocytes, play a pivotal role in regulating hypothalamic GnRH secretion via the production of prostaglandin E2 (PGE2), a key gliotransmitter that facilitates GnRH release (Sharif et al., 2013). PGE2-mediated activation of GnRH neurons is critical for maintaining the hypothalamic-pituitary-gonadal (HPG) axis and sustaining testosterone homeostasis. However, ibuprofen's anti-inflammatory action disrupts astrocytic PGE2 synthesis, leading to impaired GnRH pulsatility, reduced LH secretion, and, consequently, inducing a testosterone deficiency (Prevot et al., 2010).

Furthermore, NSAIDs have been classified as endocrine-disrupting chemicals (EDCs) due to their ability to influence fetal development and exert transgenerational effects (Jensen et al., 2016). Disruption in fetal testosterone production has been associated with long-term consequences on male reproductive health, potentially affecting subsequent generations through epigenetic modifications and altered developmental programming (Dean et al., 2018). Given the widespread use of ibuprofen and its accessibility as an over-the-counter medication, understanding its broader implications for neuroendocrine function and reproductive health is critical. This paper explores the molecular mechanisms underlying ibuprofen-induced endocrine disruption, emphasizing the interplay between neuroinflammation, astrocytic function, and steroidogenesis (**Table 1**).

Table 1: Each NSAID medication is associated with a unique mechanism that influences the steroidogenic pathway leading to interruption of important hormonal production. Inhibition of the COX enzymes impedes the hypothalamic production of GnRH while Naproxen suppresses the release of FSH and LH from the anterior pituitary.

NSAID Medication	**Mechanism of Hormonal Disruption**
Ibuprofen	Inhibits PGE2 synthesis, suppresses SF-1, reduces testosterone production.
Aspirin	Reduces androgen receptor expression, alters estrogen metabolism.
Naproxen	Suppresses LH and FSH secretion, disrupts steroidogenesis.
Diclofenac	Inhibits COX enzymes, reduces PGE2, disrupts GnRH secretion.
Indomethacin	Alters Leydig cell function, decreases testosterone synthesis.
Celecoxib	Selective COX-2 inhibition, reduces prostaglandin signaling affecting HPG axis.

Inflammation downregulates GnRH

Inflammation, COX (Cyclooxygenase), PGE_2 (Prostaglandin E_2), EP_2 (Prostaglandin E_2 receptor 2), and GnRH (Gonadotropin-Releasing Hormone) are all interconnected and influence the hypothalamic-pituitary-gonadal (HPG) axis (**Chart 1**). When inflammation occurs, it activates COX-1 and COX-2 enzymes, which convert arachidonic acid into prostaglandins like PGE_2, a key player in inflammation, fever, and immune regulation (Smith et al., 2011). PGE_2 works through four different receptors (EP1, EP2, EP3, and EP4), with the EP2 receptor playing a major role in signaling by increasing cAMP and activating protein kinase A (PKA) (Sugimoto & Narumiya, 2007). In the hypothalamus, PGE_2 acts through EP2 to influence the release of GnRH, the hormone that controls reproductive function by stimulating the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary (Brennan et al., 2020).

Under normal conditions, PGE_2 helps stimulate GnRH release, supporting fertility and hormone balance (Ojeda et al., 2006). However, prolonged inflammation—common in chronic diseases, infections, and metabolic disorders—can lead to excessive COX-2 and PGE_2 activation, disrupting normal GnRH signaling. This can result in **hypogonadotropic hypogonadism**, a condition where LH and FSH levels drop, leading to reproductive dysfunction (Rivier, 1995). Additionally, inflammatory cytokines like TNF-α, IL-1β, and IL-6 can directly suppress GnRH neurons or make them less responsive to normal signals (Dorfman et al., 2003). To counteract these effects, **COX-2 inhibitors** like celecoxib and meloxicam may help lower PGE_2 levels and prevent inflammation-related reproductive suppression (Ricciotti & FitzGerald, 2011).

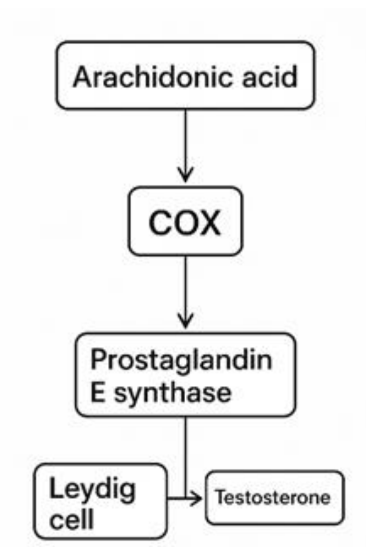

Chart 1: Under normal circumstances Arachidonic acid produces Cox-2 which stimulates PGE2 production that regulates the cell surface transcriptional signal for nuclear production of testosterone. This is lost as an effect of NSAIDs.

Impact on Leydig Cells

Leydig cells in the testes are responsible for the biosynthesis of testosterone, a process primarily regulated by luteinizing hormone (LH) through the activation of cyclic AMP (cAMP)-dependent signaling pathways. This pathway stimulates the expression of key steroidogenic enzymes required for testosterone synthesis, including steroidogenic acute regulatory protein (StAR), cytochrome P450 side-chain cleavage enzyme (CYP11A1), and 17β-hydroxysteroid dehydrogenase (HSD17B) (Payne & Hales, 2004).

Ibuprofen has been shown to impair Leydig cell function by disrupting steroidogenic gene expression. Specifically, it reduces the transcription of StAR, a critical transport protein that facilitates the movement of cholesterol into mitochondria, the rate-limiting step in steroidogenesis (Bauer et al., 2018). The downregulation of StAR compromises the availability of cholesterol for conversion into pregnenolone, thereby diminishing the synthesis of downstream androgens, including testosterone (Kristensen et al., 2018). Additionally, ibuprofen suppresses the activity of CYP11A1, further inhibiting testosterone biosynthesis at the enzymatic level (Jensen et al., 2016).

Beyond direct effects on steroidogenic pathways, ibuprofen-induced inhibition of prostaglandin E2 (PGE2) production may further impair Leydig cell function. PGE2, produced by testicular macrophages and Sertoli cells, has been implicated in modulating Leydig cell steroidogenesis by enhancing LH receptor sensitivity and cAMP signaling (Wang et al., 2013). By attenuating PGE2 synthesis, ibuprofen disrupts paracrine signaling essential for optimal Leydig cell function, exacerbating testosterone suppression (Sharif et al., 2013).

These findings suggest that ibuprofen-induced endocrine disruption occurs at multiple levels, including transcriptional suppression of steroidogenic genes, interference with mitochondrial cholesterol transport, and disruption of glial and paracrine signaling pathways that modulate LH responsiveness. Given the widespread use of ibuprofen, further research is necessary to elucidate the long-term implications of NSAID-induced suppression of Leydig cell function on male reproductive health.

Downregulation of Steroidogenic Enzymes

Ibuprofen has been shown to disrupt testosterone biosynthesis by downregulating the transcription of key steroidogenic enzymes, including 17β-hydroxysteroid dehydrogenase (17β-HSD) and cytochrome P450 17A1 (CYP17A1). These enzymes play crucial roles in androgen production within Leydig cells. 17β-HSD catalyzes the final step in testosterone synthesis, converting androstenedione into bioactive testosterone, while CYP17A1 mediates the conversion of pregnenolone and progesterone into androgen precursors such as dehydroepiandrosterone (DHEA) and androstenedione (Payne & Hales, 2004).

Studies indicate that ibuprofen decreases the mRNA expression of both 17β-HSD and CYP17A1, leading to lower circulating testosterone levels and impaired androgen production (Kristensen et al., 2018). The suppression of CYP17A1 activity not only reduces testosterone synthesis but also limits the availability of precursors necessary for downstream steroidogenesis, further compounding endocrine disruption.

The downregulation of these enzymes appears to be mediated by ibuprofen's inhibition of steroidogenic factor-1 (SF-1), a nuclear receptor critical for the transcriptional regulation of multiple steroidogenic genes (Bastien et al., 2018). SF-1 plays a pivotal role in maintaining Leydig cell function, and its inhibition by ibuprofen results in decreased promoter activity for genes encoding 17β-HSD, CYP17A1, and other steroidogenic enzymes (Jensen et al., 2016).

Furthermore, ibuprofen's anti-inflammatory effects may indirectly contribute to the suppression of these enzymes by reducing prostaglandin E2 (PGE2) levels. PGE2 has been shown to enhance the transcription of steroidogenic genes through cAMP-dependent pathways (Sharif et al., 2013). By attenuating PGE2 production, ibuprofen may further dampen the expression of 17β-HSD and CYP17A1, thereby exacerbating testosterone deficiency.

These findings highlight the multifaceted mechanisms by which ibuprofen disrupts steroidogenesis, emphasizing the need for further research to fully understand the long-term consequences of NSAID-induced endocrine dysregulation.

Modulation of Transcription Factors

The regulation of steroidogenesis is highly dependent on key transcription factors, including steroidogenic factor-1 (SF-1) and cAMP response element-binding protein (CREB), which coordinate the expression of genes necessary for testosterone biosynthesis. SF-1 is a nuclear receptor that serves as a master regulator of steroidogenic gene expression, directly controlling the transcription of StAR, CYP17A1, and 17β-HSD, all of which are crucial for androgen production (Luo et al., 1994). CREB, a pivotal transcription factor activated by cAMP-dependent signaling, enhances the expression of SF-1, thereby amplifying its role in testosterone synthesis (Manna et al., 2003).

Ibuprofen has been shown to interfere with these regulatory pathways by suppressing SF-1 activity, thereby reducing the transcriptional activation of steroidogenic genes (Jensen et al., 2019). The inhibition of SF-1 not only impairs the expression of StAR—the rate-limiting factor in steroidogenesis—but also downregulates CYP17A1 and 17β-HSD, further disrupting testosterone biosynthesis (Bastien et al., 2018). Moreover, ibuprofen's suppression of CREB phosphorylation leads to decreased SF-1 transcription, exacerbating the downregulation of critical steroidogenic enzymes (Payne & Hales, 2004).

In addition to its direct effects on transcription factors, ibuprofen-induced suppression of prostaglandin E2 (PGE2) may contribute to the inhibition of SF-1 and CREB activity. PGE2, acting through EP2 receptors, enhances cAMP production, thereby promoting CREB phosphorylation and SF-1 activation (Sharif et al., 2013). By reducing PGE2 levels, ibuprofen disrupts this pathway, further impairing the transcriptional regulation of testosterone biosynthesis.

These findings suggest that ibuprofen exerts its endocrine-disrupting effects through a multifaceted mechanism involving the suppression of key transcription factors, ultimately leading to a decline in testosterone production. Given the widespread use of NSAIDs, further research is needed to elucidate the broader implications of ibuprofen-induced transcriptional dysregulation on male reproductive health.

NSAIDs as Endocrine Disrupting Chemicals and Transgenerational Effects

Nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, have been increasingly recognized as endocrine-disrupting chemicals (EDCs) due to their ability to interfere with hormone signaling pathways at multiple levels. EDCs exert their effects by modulating hormone synthesis, receptor activity, and downstream gene expression, ultimately disrupting endocrine homeostasis (Diamanti-Kandarakis et al., 2009).

Research indicates that prenatal exposure to NSAIDs can induce long-term hormonal imbalances in offspring, potentially affecting reproductive function across multiple generations (Ergang et al., 2020). These effects are largely mediated through epigenetic modifications, including DNA methylation, histone modifications, and microRNA regulation, which permanently alter gene expression patterns in fetal tissues (Skinner et al., 2010). For example, studies have demonstrated that NSAID exposure during fetal development downregulates genes involved in steroidogenesis while upregulating inflammatory pathways, leading to persistent dysregulation of testosterone biosynthesis in adult offspring (Jensen et al., 2016).

Furthermore, NSAID-induced epigenetic alterations have been shown to affect germline cells, suggesting that reproductive dysfunction may not be limited to directly exposed individuals but may also be transmitted to subsequent generations (Nilsson et al., 2018). These transgenerational effects may manifest as delayed puberty, reduced fertility, and altered testicular development, mirroring the endocrine disruptions observed in the first-generation offspring (Kristensen et al., 2018).

Given the widespread and chronic use of NSAIDs, particularly during pregnancy, the potential for transgenerational endocrine disruption raises significant public health concerns. Future research is needed to elucidate the precise molecular mechanisms underlying these effects and to assess the long-term reproductive and metabolic consequences of NSAID exposure across multiple generations.

Maternal Exposure and Fetal Development

When pregnant women take NSAIDs, including ibuprofen, these drugs can readily cross the placental barrier, directly exposing the developing fetus to hormonal disruption (Bourgeois et al., 2016). This in utero exposure occurs during critical windows of fetal development when androgen signaling is essential for the differentiation and maturation of the male reproductive system. Disruptions in androgen action during this period can have lifelong consequences for reproductive function.

One well-established marker of fetal androgen exposure is anogenital distance (AGD), which is determined by androgen levels during early gestation. Studies have linked prenatal ibuprofen exposure to reduced AGD in male offspring, a biomarker of impaired testosterone action during fetal development (Shultz et al., 2021). Shortened AGD has been associated with cryptorchidism, hypospadias, reduced sperm count, and infertility in adulthood (Kristensen et al., 2018).

The mechanisms underlying NSAID-induced reproductive disruption appear to involve direct inhibition of testosterone biosynthesis in fetal Leydig cells. Research indicates that ibuprofen downregulates steroidogenic enzymes such as CYP17A1 and 17β-HSD, reducing testosterone production at a critical stage of male sexual differentiation (Mazaud-Guittot et al., 2013). Additionally, ibuprofen may impair the function of prostaglandin E2 (PGE2), a key mediator in fetal testicular development, further compounding androgen deficiency (Dean et al., 2018).

Beyond immediate fetal effects, epigenetic modifications induced by NSAID exposure in utero may lead to persistent reproductive dysfunction into adulthood (Ergang et al., 2020). Alterations in DNA methylation and histone acetylation in steroidogenic genes may program the developing reproductive system for long-term endocrine dysregulation, increasing the risk of infertility, testicular dysgenesis syndrome, and other reproductive disorders (Nilsson et al., 2018).

Given the prevalence of NSAID use during pregnancy, these findings highlight a critical need for further research and public health awareness regarding the potential long-term consequences of ibuprofen exposure on male reproductive health.

Transgenerational Epigenetic Effects

Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNAs, play a crucial role in mediating the long-term impact of NSAID exposure on reproductive health. These modifications do not alter the genetic code itself but regulate gene expression, potentially leading to persistent endocrine disruptions across multiple generations (Skinner et al., 2010).

Animal studies suggest that prenatal exposure to NSAIDs, such as ibuprofen, induces heritable epigenetic alterations in germ cells, which can be passed down to offspring even in the absence of direct exposure

(Smith et al., 2022). This transgenerational inheritance raises concerns about the widespread use of NSAIDs during pregnancy, particularly given their potential to reprogram steroidogenic pathways in ways that may predispose future generations to infertility, testicular dysgenesis syndrome, and other endocrine-related disorders (Nilsson et al., 2018).

One proposed mechanism involves NSAID-induced DNA methylation changes in genes regulating steroidogenesis and hypothalamic-pituitary-gonadal (HPG) axis function. Studies have shown that exposure to NSAIDs silences key genes such as StAR, CYP17A1, and 17β-HSD, reducing testosterone synthesis and impairing reproductive function in both first- and second-generation offspring (Jensen et al., 2016). Additionally, ibuprofen has been linked to histone modifications that alter chromatin accessibility, leading to dysregulated gene expression patterns that persist across generations (Ergang et al., 2020).

Non-coding RNAs, such as microRNAs (miRNAs), may also mediate transgenerational effects by modulating mRNA stability and translation of steroidogenic genes (Grandjean et al., 2019). Changes in miRNA expression profiles in response to NSAID exposure have been detected in fetal testicular tissue, suggesting that these regulatory RNAs may contribute to long-term reproductive dysfunction (Dean et al., 2018).

The potential for NSAIDs to induce epigenetic reprogramming in germ cells underscores serious public health implications, particularly given the widespread use of these medications. Further research is needed to determine the full scope of transgenerational endocrine disruption, assess human relevance, and develop guidelines for NSAID use during pregnancy to mitigate potential reproductive risks for future generations.

Clinical Implications

Long-term ibuprofen use has been associated with compensated hypogonadism, a condition characterized by elevated luteinizing hormone (LH) levels in response to reduced testosterone production. This compensatory mechanism suggests that ibuprofen-induced suppression of steroidogenesis disrupts the hypothalamic-pituitary-gonadal (HPG) axis, leading to persistent hormonal dysregulation (Ergang et al., 2020). Chronic NSAID exposure may impair GnRH pulsatility, thereby reducing LH bioactivity and ultimately compromising Leydig cell function (Kristensen et al., 2018).

Clinical studies on athletes and chronic pain patients suggest that regular ibuprofen use may contribute to decreased muscle mass, reduced libido, erectile dysfunction, and impaired fertility (Shultz et al., 2021). Given that testosterone plays a vital role in muscle protein synthesis and overall metabolic health, long-term NSAID use could have broader systemic consequences, including increased fat accumulation, sarcopenia, and reduced physical performance (Bastien et al., 2018).

Moreover, the potential for transgenerational endocrine disruption raises additional concerns about the widespread use of ibuprofen, particularly during pregnancy. The evidence that NSAIDs can cross the placental barrier and disrupt fetal steroidogenesis suggests that maternal ibuprofen use may increase the risk of reproductive disorders in male offspring (Dean et al., 2018). Given the epigenetic mechanisms underlying these effects, these reproductive abnormalities may persist across multiple generations (Smith et al., 2022).

Considering the widespread accessibility of ibuprofen as an over-the-counter medication, greater awareness of its endocrine-disrupting properties is critical for both healthcare providers and the general public. Future clinical research should focus on identifying safe usage thresholds, assessing long-term reproductive risks, and evaluating potential strategies to mitigate ibuprofen-induced endocrine dysfunction.

Therapeutic Strategies for Restoration of Steroidogenesis

The current therapeutic dilemma centers on how to effectively resolve neuroinflammation to restore and protect central and peripheral steroidogenesis, including neurosteroid production within the brain, and androgen synthesis in Leydig and thecal cells. Chronic neuroinflammation is known to impair the hypothalamic-pituitary-gonadal (HPG) axis by disrupting glial-derived prostaglandin E2 (PGE2) signaling, attenuating GnRH pulsatility, and suppressing luteinizing hormone (LH)-driven steroidogenic output. In addition, systemic inflammation and oxidative stress impair the transcription of key enzymes such as StAR, CYP17A1, and 17β-HSD, further compromising testosterone synthesis at the gonadal level.

Emerging evidence supports the use of selenium as a redox-modulating agent to combat this disruption. Specifically, selenium supplementation at 200 mcg twice daily for 8 weeks has been shown to reverse oxidative inactivation of cyclooxygenase-2 (COX-2) and normalize PGE2 production, a critical gliotransmitter involved in stimulating GnRH release and downstream LH production. This redox-mediated restoration of PGE2 levels has been linked to reinstated transcriptional activity of steroidogenic genes and enhanced testicular testosterone synthesis (Shama et al., 2020).

In parallel, selective estrogen receptor modulators (SERMs) such as clomiphene citrate and enclomiphene citrate have demonstrated effectiveness in restarting hypothalamic GnRH secretion by antagonizing negative estrogen feedback at the hypothalamic level. This results in an upregulation of pituitary LH and FSH secretion, subsequently stimulating Leydig and thecal cell androgen production. Beyond central action, SERMs have been shown to increase the sensitivity of gonadal androgen receptors, thereby potentiating the effect of circulating LH and enhancing endogenous testosterone output (Kang et al., 2022).

The combined therapeutic use of selenium to restore redox balance and neuroimmune function, and SERMs to reengage central reproductive signaling, offers a synergistic approach to rehabilitate both neurosteroidogenesis and gonadal steroidogenesis. This dual-target strategy may be particularly effective in conditions characterized by chronic neuroinflammation, oxidative stress, and suppressed HPG axis activity, such as in post-TBI hypogonadism, metabolic inflammation, and NSAID-induced endocrine suppression.

Conclusion

A growing body of evidence indicates that ibuprofen exerts suppressive effects on testosterone production through the transcriptional downregulation of key steroidogenic genes and the inhibition of regulatory transcription factors essential for steroidogenesis. By disrupting the hypothalamic-pituitary-gonadal axis, ibuprofen interferes with Leydig cell function, GnRH signaling, and prostaglandin E2 production, ultimately leading to compensated hypogonadism and reduced androgen availability.

Furthermore, the classification of NSAIDs as endocrine-disrupting chemicals (EDCs) raises significant concerns about their transgenerational effects, particularly in the context of prenatal exposure and epigenetic modifications. Studies suggest that ibuprofen-induced alterations in DNA methylation, histone modifications, and non-coding RNA expression may predispose offspring to long-term reproductive dysfunction, with potential consequences spanning multiple generations.

While short-term NSAID use is generally considered safe, the risks associated with chronic or high-dose ibuprofen exposure necessitate greater awareness among healthcare providers, researchers, and the general public. Given the widespread accessibility of ibuprofen as an over-the-counter medication, there is an urgent need to reassess its long-term safety profile, particularly in vulnerable populations such as in the military, athletes, chronic pain patients, and pregnant women.

Future research should focus on determining the reversibility of ibuprofen-induced endocrine disruption, identifying biomarkers of early dysfunction, and exploring potential therapeutic interventions to mitigate these effects. Investigating the role of anti-inflammatory alternatives and targeted strategies to counteract NSAID-induced steroidogenic suppression may provide new avenues for safer pain management without compromising reproductive health.

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Addendum A : NSAIDs

Drug Name
diclofenac systemic (Pro) **Brand names:** Cambia, Cataflam, Lofena, Voltaren, Xiclo, Zipsor, Zorvolex
diflunisal systemic (Pro) **Brand name:** Dolobid
esomeprazole / naproxen systemic (Pro) **Brand name:** Vimovo
etodolac systemic (Pro)
fenoprofen systemic (Pro) **Brand names:** Fenopron, Fenortho, Nalfon
flurbiprofen systemic (Pro) **Brand name:** FlurbiPro
ibuprofen systemic (Pro) **Brand names:** A-G Profen, Addaprin, Advil, Advil Children's, Advil Infant's Concentrated Drops, Advil Junior Strength, Advil Liqui-Gels, Advil Migraine, Caldolor, Children's Motrin, Genpril, IBU-200, Midol IB, Motrin, Motrin Childrens, Motrin IB, Motrin Infant Drops, Motrin Migraine Pain, NeoProfen, Nuprin, Proprinal
indomethacin systemic (Pro) **Brand names:** Indocin, Indocin SR, Tivorbex
ketoprofen systemic (Pro) **Brand name:** Kiprofen
meloxicam systemic (Pro) **Brand name:** Mobic
nabumetone systemic (Pro) **Brand name:** Relafen DS
naproxen systemic (Pro) **Brand names:** Aflaxen, Aleve, Aleve Back and Muscle Pain, All Day Pain Relief, All Day Relief, Anaprox-DS, EC-Naprosyn, Flanax Pain Reliever, Midol Extended Relief, Naprelan, Naprosyn
oxaprozin systemic (Pro) **Brand names:** Coxanto, Daypro
piroxicam systemic (Pro) **Brand name:** Feldene
sulindac systemic (Pro) **Brand name:** Clinoril
tolmetin systemic (Pro) **Brand name:** Tolectin DS