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Review Article

The effeminizing effect of opioids- A Review

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ABSTRACT

Opioids are pivotal therapeutics in management of escalated chronic pain (moderate-severe). The increased prescription and usage duration of opioids in last two decades shed the light on opioid-induced endocrinopathy. Opioid-induced hypogonadism (OHG) results upon long-term opioid therapy. Clinically, patients with OHG are presented mainly by sexual dysfunction and infertility. Opioid clinical use in pain therapy is indispensable. However, the resultant sexual endocrinopathy cannot be overlooked and hence replacement hormonal therapy and patient continual follow-up are important measures to ensure therapeutic compliance and secure patient's satisfaction of a good life quality.

Keywords: Opioids, chronic pain, opioid-induced hypogonadism.

INTRODUCTION

Opium-dried latex of poppy plant; *Papaver somniferum*- is the natural source of morphine and the base structure for manufacturing semisynthetic and synthetic narcotic analgesics such as morphine and codeine (Cortazzo MH, 2008; Al-Hasani R, 2011). Almost all classes of opiate substances both natural and synthetic carry high propensity of addictive properties Morgan MM (2011). Morphine, codeine, oxycodone, propoxyphene, hydrocodone and hydromorphone are commonly prescribed opioids to alleviate pain. Additionally, some opioids have been used to suppress dry coughs and to treat diarrhea, for example codeine and diphenoxylate (Stolberg VB, 2011). However, opioid therapeutic usage is associated with suppression of gonadal function in both genders. Recently, the use of opioids in the management of chronic pain and palliative care therapy shows marked rise; especially in developed countries (Michael RVK, 2013) and this is associated drug related complications also rise and affect negatively on qualtiy of life of patients.

In this narrative review, the primary objective is to analyze the available literature on this aspect of opioid therapy and explaining the possible mechanism of gonadal suppression with opioids with considering the role of the compensatory hormonal therapy in these patients. To start with we briefly discussed the general chemical and pharmacological properties of opioids, including post-receptor mechanisms and possible site of interaction the suppression of gonadal hormone synthesis. Finally, we provide the clinical features and possible therapeutic methods for opioid induced hypo-gonadism.

ENDOGENOUS OPIOID LIGANDS AND RECEPTORS

Several distinct families of endogenous opioid peptides have been identified, principally the enkephalins, endorphins, and dynorphins and they are sharing several common properties (Al-Hasani R, 2011).

Opioid receptors are expressed in pain-modulating descending pathway which includes the medulla locus coeruleus and peri-aqueductul grey area and also located in limbic, midbrain and cortical structures. The opioid peptides and their receptors are expressed throughout the nociceptive, reward and emotion neuronal circuit in the central nervous system. Apart from their highest efficacy as analgesics, the opioids cause mood enhancement and activation of dopamine mediated reward pathways (Al-Hasani R, 2011).

The opioid receptors belong to G-protein coupled receptors (GPCR), which are membrane bound proteins that mediate analgesia as well as substance abuse with opioid agents Freye E, 2008). There are three classical main receptors (mu, kappa and delta) to mediate analgesia in experimental models and the role of fourth one (nociception or orphanin FQ receptor) in mediation of analgesia is not well described (Stevens CW, 2009).

Opioid receptor subtypes are defined by multiple studies, by illustrating drug effect at diverse functional sites and drug-pharmacological profile of opioids. Based on definition and sensitivity to naloxone, three classical subtypes-(μ; MOP), (κ; KOP) and (δ; DOP) exits and later with low-stringency hybridization screening using opioid receptor probes led to identification of a fourth "Opioid like receptor" and following the identification of an endogenous ligand, it is named as "Nociceptin/Orphanin FQ peptide receptor" (NOP) and classified as a non-opioid subtype of the opioid receptor family owing to insensitivity to naloxone but having a significant sequence homology with classical opioid receptor (Mc Donald J, 2016).

Signalling Mechanisms Involved with Opioid Receptor

All four subtypes of opioid receptors are 7-transmembrane spanning proteins, that couples to inhibitory G-protein. On activation with an agonist, Gα and Gβγ subunits dissociates and interact with various subcellular pathways to stimulate GTPase activity and to inhibit the generation of cyclic adenosine monophosphate (cAMP), which is found to be a Gα dependent process (Al-Hasani R, 2011).

The most significant process of post receptor opioid signal transduction relates to their modulation calcium and potassium ion channels. The Gα subunits dissociated from Gβγ, interacts with the G-protein gated inward rectifying K^+ channel, Kir^3 and inactivates the channel, following the hydrolysis of GTP to GDP to cause cellular hyperpolarization and inhibits the neuronal tonic activity (Bourinet E, 1996; Zamponi GW, 1998; Zamponi GW, 2002).

Chemical Classification of Opioids

Opioids are classified into three categories according to the source opioid-derived, which are (a) natural opiates: these are alkaloids found extracted from poppy seeds e.g., morphine, codeine, and opium, (b) semisynthetic opiates: opium is chemically modified for the synthesis of these drugs e.g., heroin, oxycodone, oxymorphone, and buprenorphine and (c) synthetic opiates: which are laboratory-manufactured e.g., fentanyl, pethidine, and dextropropoxyphene (Stolberg VB, 2011). There are various structural characteristics for opioids according to base chemical model such as phenanthrenes, benzomorphans, diphenylpropylamines, phenylpiperidines, anilidopiperidines, oripavine and morphinan derivatives (Mc Donald J, 2016). In addition, some synthetic opioids are not belonging to the above mentioned categories such as tramadol (Stolberg VB, 2011).

PHARMACOKINETIC AND PHARMACODYNAMIC CHARACTERISTICS OF OPIOIDS

Opioids differ by the way they are metabolized, and patients differ in their ability to metabolize individual opioids (Lotsch J et al., 2002) Most opioids incur extensive hepatic first-pass metabolism before reaching the systemic circulation. Due to lipophilicity, opioids traverse cell membranes to their target tissues (Clementi F, 2015; Schiff D, 2008). Opioid metabolism takes place primarily in the liver through both phase 1 and phase 2 metabolism (Smith HS, 2009). Phase 1 metabolism by oxidation or hydrolysis of the drug mainly by cytochrome P450 (CYP). Furthermore, Phase 2 metabolism makes the drug more hydrophilic through its conjugation to glucuronic acid, sulfate, glycine, or glutathione (Smith HS, 2009). For certain opioids, the specific metabolic pathway involved has important clinical implications in terms of active metabolites (e.g., morphine, meperidine) or an ultra-short duration of action (e.g., remifentanil). Individual genetic variation in the metabolic pathway can drastically alter the clinical effects of opioid agents (e.g., codeine) (Smith HS, 2009). The neurochemical effects of acute and chronic opiate administration are multiple and complex. There is some evidence that a limited number of these changes may contribute to sensitization, tolerance, and withdrawal, but establishment of the addicted state has yet to find molecular correlates (Jayaram-Lindstrom N, et al., 2017).

Opioid systems play a major role in the modulation of pain behavior and antinociception (Al-Hasani R, 2011; Feng Y 2012). The original classification of opioid receptors entails Mu (μ), kappa (κ), and delta (δ) subtypes (Preedy VR, 2016). The recently characterized opioid receptor like-1 (ORL1) whose function is relatively off the classical opioid receptors (Freye E, 2008). Theprototype ligands of mu, kappa and delta receptors are morphine, ketocyclazocine and enkephalin respectively (Al-Hasani R, 2011). Opioids can act as agonists, antagonists or partial agonists at their receptors (Preedy VR, 2016). The pharmacological action of opioids is mediated by opioid receptors located primarily in brain and spinal cord regions involved in the transmission and modulation of pain (Pardo M, 2017). Binding of opioid agonists with their receptors (GPCR) leads primarily to reduction of

neuronal excitability due to hyperpolarization of the cell (Pardo M, 2017).

Opioids exert their therapeutic effects at multiple sites with various pharmacodynamic effects. They inhibit the release of substance P from primary sensory neurons in the dorsal horn of the spinal cord, mitigating the transfer of painful sensations to the brain. Opioid actions in the brainstem modulate nociceptive transmission in the dorsal horn of the spinal cord through descending inhibitory pathways (Matthies BK, 1992). Furthermore, morphine induces signal changes in "reward structures" in human brain (Becerra L, 2006). While Mu opioids represent the most effective analgesics, they are also mood enhancers and euphoric through activation of central dopamine reward pathways (Al-Hasani R, 2011). Furthermore, studies on genetically-altered mice showed important information about opioid receptor function. In μ opioid receptor knockout mice, morphine-induced analgesia, reward effect, and withdrawal effect are absent (Feng Y, 2012; Sora I, et al. 1997). Importantly, μ receptor knockout mice also fail to exhibit respiratory depression in response to morphine (Dahan A, et al. 2001).

Opioids and their Therapeutic effects

Opioids are the mainstay therapeutics used in treatment of moderate to severe pain from different pathogenic origins; surgical, palliative cancer and/or inflammatory pain (Carmona Bayonas A, 2017; Rasor J, 2005; Baumann S, 2009; Furlan AD, 2006). Additionally, opioid maintenance therapeutic regimens are indispensable in cases of opioid-dependence (Yee A, et al. 2018; Yee A, 2014; Bawor M, et al. 2014; Lugoboni F, 2017). Although opioids may be excellent analgesics, they are often used as second choice treatment of chronic pain, mainly because of high degree of drug related complications. However, it is not uncommon to combine opioid treatment with other modalities, including psychological treatment and physical rehabilitation. Simultaneously, interventional pain procedures and adjunctive analgesics may be useful as well (Cortazzo MH, 2008; Meyer R, 2014; Overholser BR, 2011). In the event of non-opioids or other analgesics failure, opioids alone or in combination have a role (Geppetti P, 2009). On the other hand, in moderate to severe cancer pain, strong opioids are the drug of choice particularly morphine (Rana SP, 2011). Both the public and physicians have long feared morphine, mainly because of the erroneous belief that its therapeutic use is intrinsically linked to abuse and addiction or severe adverse reactions (Akbarabadi A, et al. 2018). In a recent clinical update for the International Association for the Study of Pain (IASP), Loeser (2012) cites the largely unknown value of opioid treatment in patients with chronic non-cancer pain as one of the major crises in pain management (Loeser JD, 2012). Michna and his co-workers (2014) compared safety and efficacy outcomes between opioids formulated with technologies designed to deter or resist tampering (i.e., abuse-deterrent formulations [ADFs]) and non-ADFs for commonly prescribed opioids for treatment of non-cancer pain in adults. They concluded that ADFs and non-ADFs had comparable efficacy and safety profiles, while both were more efficacious than placebo in reducing pain intensity (Michna E, 2014).

THE EFFECT OF OPIOIDS ON THE SECRETION OF TESTOSTERONE

Morphine therapy causes a prolonged suppression of testosterone secretion, which lasts along with opioid therapy, in both males and females and reaches castration level of <1 ng/mL after a few hours of initiation of therapy (Aloisi AM, 2005). However, the level of testosterone recovers within days of discontinuation of opioid therapy (Smith HS, 2012). This reduction of testosterone secretion is mainly attributed to opioid induced suppression of GnRH release from hypothalamus (Daniell HW, 2006). Additionally, central mechanism of androgen suppression, opioid causes demonstrable alteration in the expression of 5 α reductase type 1 and/or P 450 aromatase mRNA in peripheral body tissues, which increases the catabolism of testosterone (Aloisi AM, 2010). In a tweleve-weeks prospective trial, Roberts and colleagues demonstrated hypothalamo-pituitary-gonadal (HPG) suppression with intra-thecal opioid administration, with reduced sexual activity and significantly diminished mean serum testosterone level in ten chronic non-cancer pain male patients (Roberts LJ, 2002). In addition to central inhibition, suppression of adrenal androgen release plays a role in opioid induced hypogonadism, which is demonstrated by Daniell HW in a case-control study with participation of 152 patients of both genders. The author measured the level of dehydroepandrosterone (DHEA) and adrenocorticotropic hormone (ACTH) in these patients and found significant reduction in DHEA without suppression of ACTH in patients on opioid therapy, which deny the role of ACTH in opioid-iduced hypogonadism (Daniell HW, 2006). A correlation exists between dose of opioid and duration of therapy with risk for the suppression of HPG axis (Daniell HW, 2002). However, the opioid induced hypogonadism is reversible on discontinuation of opioid, even among long term therapy (Daniell HW, 2002; Elliott JA, 2011; Finch PM, 2000).

Pathophysiology and clinical features of Opioid-Induced Hypogonadism (OHG)

Opioids procure common adverse effects such as constipation, respiratory depression and dependence/ abuse susceptibility (Khademi H, 2016). The increased prescription and usage duration of opioids in last two decades shed the light on opioid-induced endocrinopathy (Manchikanti L, 2012; Demarest SP, 2015; Carmona Bayonas A, 2017; Aloisi AM, 2011; Policola C, 2014). Opioid-induced hypogonadism (OHG) results upon long-term opioid therapy (≥ 4weeks) (Nenke MA, 2015). However, clinical studies on surgical patients reported acute occurrence of OHG (few hours after commencing opioid therapy) (Policola C, 2014; Brennan MJ, 2013; Chrastil J, 2014). Clinically, patients with OHG are presented by fatigue, depression, muscle wasting, decreased bone-mineral density, sexual dysfunction and infertility (Demarest SP, 2015; Carmona Bayonas A, 2017).

Sex hormones in males and females are under control of hypothalamo-pituitary-gonadal axis (HPG). OHG is attributed to derangement of the pulsatile release of hypothalamic GnRH with consequent deficiency of luteinizing hormone (LH) follicle-stimulating hormone (FSH), estrogen, progesterone and androgens (Delitala G, 1983; Santen FJ, 1975). Using naloxone in farm animals increases the frequency of GnRH pulses with increased levels of LH (Barb CR, 1991; Petraglia F, 1986). Similar data were obtained on an experimental study on rats showing the improvement of LH secretion due to improvement of the GnRH pulse generator by naloxone (Funabashi T, 2010). Furthermore, murine studies demonstrated that morphine reduces serum testosterone by increasing expression of mRNA of (a) testosterone metabolizing enzyme aromatase which enhances conversion of testosterone into estradiol and (b) 5-alpha reductase an enzyme facilitate conversion of testosterone into dihydrotestosterone (Aloisi AM, 2010; Amini H, 2005).

OHG is presented differently in patients but sexual dysfunction affects ~76% and 64% in males and females respectively (Palha AP, 2002; Brown RT, 2007; Yee A, 2014). A study of sexual dysfunction of opioid addicts seeking medical care, showed that 50-81% of them suffering from erectile dysfunction (2016). Furthermore, studies in patients on methadone maintenance therapy (MMT) showed that erectile dysfunction is a major complaint which negatively impact patient's quality of life and subsequently medication compliance (Yee A, 2018; Yee A, 2014; Reddy RG, 2010; Elliott JA, 2012; Abs R, 2000; Aloisi AM, 2009). Human study on patients (male and females) receiving intrathecal opioid for non-cancer pain showed that 96% of men suffer impotence which is associated with testosterone deficiency (Aggarwal N, 2016; Abs R, 2000). OHG may also be presented in both sexes as diminished sex drive, dysfunctional orgasm and postsexual un-satisfaction (Brennan MJ, 55; Abs R, 2000). Using oral sustained release opioid in patients with non-cancerous pain showed sexual dysfunction with subnormal serum levels of testosterone, estradiol and LH (Daniell HW, 2002).

There is insufficient data on OHG in women. Intrathecal opioids in pre-menopausal women showed manifestations of hypogonadism presented mainly as decreased libido [69%], oligomenorrhoea [100%] and infertility (Demarest SP, 2015; Abs R, 2000; Aloisi AM, 2009). Of clinical importance, during opioid therapy hypogonadism screening and treatment by reducing opioid dose or testosterone replacement therapy is essential to protect patients from OHG (Yee A, 2018; Rhodin A, 2010; Aloisi AM, 2011; Duarte RV, 2013). Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are prohormones produced by adrenal cortex under control of pituitary adrenocorticotrophic hormone (ACTH). Opioid therapy reduces hypothalamic corticotropin-releasing hormone (CRH) through kappa-opioid receptors and results in deficient adrenal production of cortisol (Pascoe JE, 2018; Hall GM, 1990), DHEA and DHEAS (Daniell HW, 2008). The main role played by DHEA and DHEAS is to be converted peripherally in tissues into sex steroids (Grossman A, 1968). They are the main source of androgens in females (controls sex drive) and estrogen in postmenopausal females.

Bone mineral density and remodeling is under crucial mechanisms involving hormonal contributory mainly sex hormones. Androgens and estradiol play a pivotal role in bone health and equilibrate bone remodeling status (Nagy V, 2015). Patients on long-term opioids are reported as more prone to fracture due to dizziness (Vestergaard P, 2006). However, other studies reported an association between OHG due to long-term intrathecal opioid in non-cancer pain and low bone density (Duarte RV, et al. 2013; Vellucci R, 2016; Gaffney CD, 2015). Furthermore, in a murine femur fracture model with OHG showed diminished callus formation and endurable healing of bone fracture (Chrastil J, 2015). Receptor Activator of Nuclear Factor κ-B (RANKL) is recently linked to bone remodeling and correlated with different mechanism to bone turnover processes (Nagy V, 2015). Martin et al, 2017 showed the inhibitory effect of estradiol and dihydrotestodterone (DHT) on RANKL association to cell membrane of pre-osteoblast an *in vitro* cell culture which led to suppression of osteoclast differentiation through non-genomic mechanisms (Martin A, 2017).

Animal studies showed that opioid therapy is associated with enhanced prolactin secretion of in both sexes (Barb CR, 1981; Petraglia F, 1986; Fitzsimmons MD, 1992). On the other hand, clinical studies demonstrated that prolactin is increased in initial

opioid therapy and this is followed by regression to normal values upon chronic opioid therapy (Abs R, 2000; Aloisi AM, 2009; Merdin A, 2016; Farag AGA, 2018). Mu-Opioid receptor agonists such as morphine and methadone are associated with manifest increase of prolactin by inhibiting dopamine release from hypothalamus (Buss T, 2014; Howlett TA, 1986). Buprenorphine is a partial opioid agonist on μ-receptors and hence have a minimal prolactin increase with its therapeutic doses (Amoroso S, 1988). Prolactin excess is associated with failure of ovulation and reduced production of GnRH which may add to OHG sexual dysfunction. Bromocriptine is a dopamine agonist and is the treatment of choice in OHG with hyperprolactinemia.

Therapeutic Strategies in Opioid Induced Hypogonadism

Following healthy life style, cognitive behavioral therapy and reducing the dose of opioids through combination therapy with NSAIDs are initial measures to improve sexual endocrinopathy associating their usage (Carmona Bayonas A, 2017; Basaria S, 2015). Additionally, using opioids of shorter duration of action is reported as beneficial precaution helping to initially avoid or improve patients sex hormone profile. Testosterone replacement therapy has been assessed in different experimental and clinical studies as regard their benefits to improve hypogonadism-associated patient complaints such as impotence and infertility (Raheem OA, 2017; Amini Lari M, et al. 2018). In a recent clinical study, testosterone-replacement therapy is found to be beneficial in improving patient's tolerance to pain and hence they required less therapeutic doses of opioids (Raheem OA, 2017). The use of testosterone as hormonal replacement is still not conclusive more clinical studies with bigger patients' samples and designs minimizing bias are still required to build an evidence-based decision (Carmona Bayonas A, 2017; O'Rourke TK, 2016). Furthermore, using selective estrogen receptor modulators "SERMs" such as clomiphene citrate are an alternative acting through improving patient's sensitivity to testosterone in both sexes (O'Rourke TK, 2016; Bendre SV, 2015). This alternative may be better choice in female patients to avoid the expected and unavoidable virializing effect of testosterone in female patients. However, Khera M 2015, reported in his review the safety of using Testosterone replacement therapy in female patients with OHG (Khera M, 2015).

In conclusion, the opioid therapy plays a major role in the management of chronic and severe pain and use of these therapeutic agents increases in palliative care medicine. Due to favourable legalization in developed countries, the quantity of percapita use of the opioid shows a positive trend. At the same time there is a hike in the incidence of drug related complications with opioids. In this review, it is evident that the opioid drug therapy induces hypogonadism both in male and females, depending on the concentration of the drug and duration of therapy. However, the opioid induced hypogonadism (OHG) is reversible on discontinuation of opioid therapy. The effect of OHG in mainly induced by the reduction in GnRH secretion from the hypothalamus and contributed by the increased peripheral catabolism of testosterone by altering the expression of 5 α reductase type 1 and/or P 450 aromatase mRNA in peripheral body tissues. It would be suggestible hormone replacement therapy in patients with long term/continuing opioid therapy to avoid such complications and to maintain better quality of life.

CONFLICT OF INTEREST

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