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Review

Sex differences and hormonal modulation of deep tissue pain

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ABSTRACT

Women disproportionately suffer from many deep tissue pain conditions. Experimental studies show that women have lower pain thresholds, higher pain ratings and less tolerance to a range of painful stimuli. Most clinical and epidemiological reports suggest female gonadal hormones modulate pain for some, but not all, conditions. Similarly, animal studies support greater nociceptive sensitivity in females in many deep tissue pain models. Gonadal hormones modulate responses in primary afferents, dorsal horn neurons and supraspinal sites, but the direction of modulation is variable. This review will examine sex differences in deep tissue pain in humans and animals focusing on the role of gonadal hormones (mainly estradiol) as an underlying component of the modulation of pain sensitivity.

1. Introduction

Chronic pain affects more people than heart disease, diabetes and cancer combined (Institute of Medicine report: Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research (2011)) and visceral pain is the number one reason patients seek medical attention (International Association for the Study of Pain: Global Year Against Visceral Pain, http://www.iasp-pain.org/Content/NavigationMenu/GlobalYearAgainstPain/GlobalYearAgainstVisceralPain/PressRelease/default.htm). Furthermore, sex matters and it is generally accepted there is a sex difference in pain and analgesia (International Association for the Study of Pain: Global Year Against Pain in Women, http://www.iasp-pain.org/Content/NavigationMenu/GlobalYearAgainstPain/RealWomenRealPain/default.htm), although the magnitude of sex differences may be small and the direction can differ depending upon many factors including type of test, peripheral organ, and genetics (including species and strain in animals). In the patient population there are significantly more pain conditions/syndromes that are more prevalent in women than men (Berkley, 1997; Greenspan and Traub, 2013). It is therefore imperative to understand what drives sex differences in deep tissue pain in order to better optimize treatment, perhaps on a sex directed basis. As such, how gonadal hormones modulate deep tissue pain is an important question.

Many excellent and informative reviews have been published on the general topic of sex differences in pain in the last 15 years (Aloisi, 2003; Berkley, 1997; Craft, 2007; Fillingim et al., 2009; Gintzler and Liu, 2012; Greenspan et al., 2007; Greenspan and Traub, 2013; Heitkemper and Jarrett, 2008; Holdcroft and Berkley, 2006; Hurley and Adams, 2008; Martin, 2009b; Mogil and Bailey, 2010; Racine et al., 2012a, 2012b; Riley et al., 1998; Unruh, 1996) and this review will not duplicate those efforts. In addition, we will not attempt to review deep tissue pain in general. Rather, the state of understanding of sex differences and the role of gonadal hormones in deep tissue pain conditions (visceral, somatic) will be examined although contrasts to superficial somatic pain will be addressed.

2. Human studies supporting a sex difference and hormonal modulation of deep tissue pain

Many chronic pain conditions involving deep tissue such as irritable bowel syndrome (IBS), fibromyalgia (FM), temporomandibular joint disorder (TMD), painful bladder syndrome/interstitial cystitis (PBS/IC), and chronic fatigue syndrome (CFS) have greater female prevalence or symptom severity (see Berkley, 1997; Fillingim et al., 2009; Greenspan and Traub, 2013; Unruh, 1996 for review). For example, women with IBS had greater abdominal pain vs. males and lower rectal discomfort thresholds than healthy

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women or men with IBS (Chang et al., 2006; Tang et al., 2012). Likewise, pain in TMD patients was greater in women compared to men (Schmid-Schwap et al., 2013). These conditions involve different peripheral organs but symptoms may coexist in the same patient (Aaron et al., 2000; Chang et al., 2003a; Kurland et al., 2006; Tietjen et al., 2010; Veale et al., 1991). Although genetic predisposition and previous psychological or physical (e.g., inflammation) challenges may contribute to the occurrence of deep tissue pain, in many cases no obvious pathophysiological signs in the peripheral tissue/nerve could be detected at the time of medical evaluation, pointing to dysregulation of central nervous system function as a potential cause of excessive pain.

2.1. Sex differences in deep tissue pain

Temporal summation (the progressive increase in response to a constant, repetitive stimulus) measures increases in central processing of nociceptive stimuli. In a recent review of experimental thermal and mechanical pain studies involving healthy volunteers, more than half of the studies reported increased temporal summation in females compared with males (Racine et al., 2012b). Another review that included patient populations and healthy volunteers reported greater temporal summation in women (Fillingim et al., 2009). Greater temporal summation of pain was observed in female TMD, lower back pain and IBS patients compared with healthy volunteers or male patients (George et al., 2007; Sarlani et al., 2007; Zhou et al., 2011). These studies indicate that central sensitization is more readily evoked in women and is further augmented in women suffering from deep tissue pain.

In contrast to temporal summation measuring pain facilitation, central pain modulation (CPM, formerly called DNIC (diffuse noxious inhibitory controls)) examines the ability of the central nervous system to inhibit pain. CPM measures the ability of a noxious conditioning stimulus to inhibit the response to a noxious test stimulus. Reduced CPM is associated with greater risk of chronic pain and comorbid pain conditions (see Lewis et al., 2012; Staud, 2012; Yarnitsky, 2010 for review).

In healthy volunteers repetitive thermal stimulation evoked temporal summation. CPM inhibited the summation in healthy men, but had no effect in healthy women (Staud et al., 2003). In contrast, a different study reported temporal summation was not reduced by a conditioning stimulus in either sex, but CPM did reduce mean pain ratings and peak pain (Tousignant-Laflamme et al., 2008). In another study, distracting and painful conditioning stimuli significantly reduced heat pain intensity and unpleasantness ratings for both sexes, with significantly larger distraction effects on intensity ratings for men than women (Quiton and Greenspan, 2007). In a model of induced muscle pain two bilateral injections of hypertonic saline into the trapezius muscle induced greater pain ratings and lower pressure pain thresholds following the second injection in women compared to men. Correspondingly, the pressure pain threshold increased in men, but not women, in an area of referred pain (Ge et al., 2004, 2006). These data were interpreted to suggest men had greater inhibitory control mechanisms. In a review of 13 studies, approximately half showed less pain inhibition in women compared to men, the remaining studies reporting no sex difference (reviewed in Fillingim et al. (2009)). These data suggest CPM may be less effective in women although how the experiments were conducted clearly affects the results.

Clinically, several studies have reported significantly less pain inhibition from CPM in women with fibromyalgia compared to healthy controls (Kosek and Hansson, 1997; Normand et al., 2011) although distraction improved the efficacy of CPM in this patient population (Staud et al., 2003). Female patients with IBS or TMD failed to show pain inhibition during CPM compared to healthy subjects and showed a different pattern of brain activation revealed by fMRI (Heymen et al., 2010; King et al., 2009; Wilder-Smith et al., 2004).

2.2. Hormonal regulation of deep tissue pain

A meta-analysis on studies of experimental pain reactivity in healthy women of reproductive age indicated women in the follicular phase had higher pain thresholds than later phases (Riley et al., 1999). A more recent review reported that increased reactivity to pain occurs during the perimenstrual phase or around ovulation (Martin, 2009a), suggesting lower levels of female gonadal hormones or rising/declining of these hormones is correlated to higher pain perception. In addition, greater CPM was observed in the ovulatory phase than during the other times of the menstrual cycle (Rezaii et al., 2012; Tousignant-Laflamme and Marchand, 2009), suggesting pain perception and the intrinsic pain inhibitory system are both regulated by female gonadal hormones in healthy pre-menopausal women.

Several studies in chronic pain patients point to a negative correlation between female gonadal hormone levels and deep tissue pain severity. For example, a population-based questionnaire indicated IBS symptom severity increased after menopause and post-menopausal women had greater abdominal pain/discomfort symptoms compared to pre-menopausal women or men (Olafsdottir et al., 2012). However, another study reported abdominal pain severity decreased in women over age 50 (Palsson et al., 2003). In pre-menopausal women abdominal pain and rectal sensitivity increased during menses in IBS patients, but not healthy women (Houghton et al., 2002). A recent review concluded there is not enough data to make a firm conclusion regarding menopause and IBS symptomatology, although this same review concluded IBS symptoms were heightened around menses (Adeyemo et al., 2010). Estrogen withdrawal from oral contraceptive regimens contributed to pelvic pain and fluctuation in estrogen levels contributed to menstrual migraine (Bitzer, 2013; Mathew et al., 2013). Similarly, TMD pain ratings increased towards the end of the menstrual cycle and peaked during menstruation when the body had the lowest estrogen and progesterone level. A second peak of pain rating occurred around the time of ovulation when there was a rapid surge in estrogen level. The latter was not seen in women using oral contraceptives (LeResche et al., 2003; Slade et al., 2011).

The modulation of fibromyalgia pain by gonadal hormones is less certain. Several studies report FM pain did not fluctuate during the menstrual cycle (Alonso et al., 2004; Okifuji and Turk, 2006; Samborski et al., 2005), although another study reported menstrual cycle effects in about 50% of patients (Pamuk and Cakir, 2005). In post-menopausal women with fibromyalgia, hormone replacement did not affect pain ratings (Stening et al., 2011). In general, there was an increase in deep tissue pain symptoms around the time of menses and early menopause, at times of declining or low ovarian hormones, suggesting that estrogen and progesterone withdrawal may contribute either directly or indirectly to pain hypersensitivity.

2.3. Brain imaging of deep tissue pain

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) measure differences/changes in brain area activation at rest and in response to tasks. It is well acknowledged that the limbic system including cingulate cortex, amygdala, hippocampal formation and other limbic related brain regions such as the insula cortex (IC) and prefrontal cortex are involved in emotion, cognition, anticipation of tasks, attention responses and arousal status of the body. Brain imaging studies indicate the