

REVIEW ARTICLE

Sex differences in pain perception and interpretation

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Abstract

This study tries to explain the importance of sex differences in the perception of pain and its treatment. The study examines sex differences not only between men and women, but more generally – between males and females. The study deals with both experimental and clinical findings. Generally speaking, women have lower pain thresholds and they also differ in their response to analgesic therapy (e.g. opioids). We focused our attention on a description of painful symptoms and syndromes, their pathophysiology and treatment. This study aims to contribute to a better understanding of the pathophysiology of chronic pain, particularly since it affects about 30% of the population. Proper treatment should be based on the pathophysiology and pharmacology of pain phenomena. The study also presents therapeutic experiences and possible clinical applications. Our article intends to promote good clinical practice based on evidence-based medicine.

INTRODUCTION

Treatment of chronic pain, which affects an average of 30% of the population, is significant in terms of medical practice. Individual medical disciplines try to develop consensus-recommended procedures (guidelines) that take into account all factors that can affect treatment. One of the important factors that can affect proper treatment of chronic pain is gender differences. In this article we analyze different pathophysiological mechanisms associated with pain perception in terms of gender differences from the standpoint of general knowledge and principles of “evidence based medicine.” Additionally, we describe the current status of pain treatment and clinical experiences. We also evaluate experimental and clinical findings in an effort to determine what new information has application in the clinical setting.

The Working Group Sex Gender and Pain – IASP (Greenspan *et al* 2007) developed a consensus report

on the study of sex differences in pain and analgesia which underlines the following principles:

- The relevance and importance of studying sex differences
- The importance of experimental studies of sex differences in pain and in analgesia
- Questions whether sex differences are due to gonadal differences. The answer is yes, but only partially
- Testing the estrous cycle in animal studies, the influence of the menstrual cycle in humans, hormonal manipulation in animal studies and in human studies
- Which types of pain are suitable for the study of sex differences in animals and humans
- Deals with clinical and psychosocial studies of sex differences in pain and analgesia
- Defines these differences: age, race, ethnicity and culture, history, the difference between patients and controls in the perception of pain, comorbidity, dis-

ability, treatment, natural variability, hope, struggles with pain, mood and other psychological factors

- Deals with the temporal summation of pain, opioid analgesia and the future of this study, which is considered relevant

We also briefly address the abovementioned issues.

This was linked to the “Global year of pain in women” (2010), which declared the IASP and proclaimed it to be a very important stage in the study of pain (Collett & Berkley 2007).

EPIDEMIOLOGY OF PAIN

When we were finishing this article, the European Journal of Pain published the study “Gender role after experimental pain responses: A systematic review with meta-analysis” by Alabas *et al* (2012a), in which the authors performed a meta-analysis of studies from years 1950–2011.

They documented the prevalence of four chronic pain conditions among 131,535 adults in Canada. The prevalence of depression in women was 9.1%, which was two times higher than in men (5%). One third of women patients suffered from chronic pain – mostly fibromyalgia, arthritis and rheumatism, back pain and migraines (Denegar *et al* 2012). The prevalence of depression in people with chronic pain was 11.3% vs. 5.3% in those without chronic pain. Depression and chronic pain are significant sources of disability, especially in women.

Tsai (2007) described large differences in depressive tendencies among Chinese adults with osteoarthritic knees. Women were more prone to depression and more often afflicted with pain than men. Women who could not walk tended to express their feelings about the problem more than men. Psychological risk is an important factor to consider before knee replacement. Pessimism has been found to make pain much worse and can delay recovery for up to two years, in some cases, after total knee arthroplasty (Tsai 2007). Normally, women recover faster after knee arthroplasty than men, although they have greater functional limitations during the surgical period; nonetheless, they heal faster than men and have better improvement scores.

RESEARCH INTO PAIN IN HUMANS

Men and women are different and this difference often manifests as physical factors such as body size and thickness of the skin, as well as different neuronal organization and density of opioid receptors. Of course, there are also psychological and cultural differences, so it is impossible to conclude that any one factor is much more important than the others.

Pain perception

Women are more sensitive to pain than men. Among 78 clinical pain states, half of them are more common

in women, and only one-third are more common in men (Berkley 1997; Fillingim *et al* 1999, 2009; Fillingim 2005). Women have lower thresholds to experimentally induced somatic pain stimuli, greater ability to discriminate between stimuli, higher pain scores, and lower tolerance to pain than men (Gallagher 2012; Pool *et al* 2007). Peripheral vasoconstriction during prolonged cold nociceptive stimulation generated more response in women than in men, which means that women may be much more sensitive to cold, but not heat stimulation, than men (Manning & Fillingim 2002).

When the threshold for mechanical pain was tested in healthy volunteers it was shown that the threshold of pain pressure points was lower in women than in men, and similar changes were also observed in fibromyalgia. Recovery after fibromyalgia pain was faster in men than in women; women are also known to go through different phases of pain relative to their menstrual cycle (Graven-Nielsen & Arendt-Nielsen 2007).

Kakeda & Ishikawa (2011) studied the effect of sweet stimuli on pain perception in adults in a randomized study. They studied 20 men and 20 women; half of them received a 24% sucrose solution and the other half received distilled water during immersion of their hand in cold water. In men, contrary to women, the sucrose solution in their mouth increased the latency of pain sensations compared to distilled water; however, tolerance to pain did not differ. This analgesic effect was particularly evident in males, which was rather surprising since women are thought to be very responsive to sweet tastes. This finding has potential use in the management of acute pain in men.

Hypoalgesia also differs between the sexes. Stress-induced modulation of pain is associated with different degrees of activation of neural and endocrine systems that are sexually dimorphic. Riva *et al* (2011) showed that it was easier to recognize pain in women from their facial expressions than in men and underestimation of pain was more common in men than in women.

Garcia *et al* (2007) measured pain thresholds using pressure points on various parts of the body. Women had lower pain thresholds compared to men. In all areas of the body, these differences were expressed more in control pressure points than at points where pain originated.

Lund & Lundberg (2010) studied gender differences in sensory and pain thresholds after electro-acupuncture application. The pain threshold after acupuncture was increased in women but unchanged in men. Inter individual variability was large in both sexes.

Age differences

There is also a difference between adults and children. Children between 6–8 years are less sensitive to all painful stimuli compared to older children, 9–12 years; on the other hand there was practically no difference compared to children 13–17 year olds. Sex differences were minimal, if any, during childhood (Blankenburg *et al* 2010).

Srivatsava *et al* (2010) describe the effect of age and gender on pressure and cold stimulation in the Indian population. They examined young adults (17–25 years old) and aging men and women (50–70 years). The protocol involved immersion of one hand in cold water (0–4°C) for one minute, during which time systolic and diastolic blood pressures were measured. The increases in systolic and diastolic blood pressures were higher in young women than in young men and the differences were more evident in diastolic pressures. Similarly, in older groups of both sexes, responses to the cold pressor test were always associated with an increase in both diastolic and systolic blood pressure but the diastolic pressure increased more in men than in women.

Painful behavior at extremely low gestational ages was measured in children with gestational ages less than 28 weeks. Several physiological parameters were measured: [1] changes in heart rate and oxygen saturation, and behavioral parameters, [2] facial expression, facial and body movements and biochemical parameters, and [3] cortisol in saliva. A heel prick was used as the pain stimulus and a change of diapers was used as the painless stimulus. Four mimic characteristics were observed: [1] facial expression with pulling eyebrows, [2] closed eyes, [3] course of nasolabial folds, and [4] vertical constriction of the mouth that appeared immediately after the heel prick. Facial expressions were the most sensitive indicator of pain in very premature infants. Other symptoms such as hands on face and yawning must be monitored in the future. In this work, no sex differences were observed in facial expression in response to pain (Ozawa *et al* 2011). The effects of gender were also monitored from the point of view of hand laterality on the development of pain in human neonates. Using imaging techniques, it has been shown that right-sided stimulation induces greater prefrontal activation than left-sided stimulation. Hand laterality therefore affects pain perception in neonates although no sex differences in pain perception have been observed during this developmental period.

Sex differences in the elderly, with regard to pain perception, were less pronounced compared to those that were middle aged.

NEUROBIOLOGICAL FACTORS AND PHARMACOTHERAPY

Opioids

Men and women differ in their sensitivity to opioid treatment. Women have lower responses to μ opioid agonists and better responses to κ opioid agonist analgesic (pentazocine) than men (Chen *et al* 2008).

Beta endorphin modulates adenosine provoked chest pain in men but not in women. In men, beta endorphin induces analgesia, while women are more resistant to modulation (Sadigh *et al* 2007).

Opioid analgesia is not only dependent on sex hormones but also on genotype. It does not affect

memory, however, when testing episodic memory, women had more errors after oxycodone than men and men had more errors after placebo than women (Friswell *et al* 2008).

A clinical study by Li *et al* (2010b) showed the effects of gender on the minimal local analgesic concentration of ropivacaine needed for local anesthesia during anorectal surgery. In women, the effective dose of anesthesia is 31% higher than in men.

When epidural morphine was used, the only side effect observed was a higher incidence of nausea and vomiting (47% women, 16% men). Women have more frequent psychological effects that accompany pain. Sensitivity, fear and pain are higher in women than in men (Frew & Drummond 2007).

Placebo effects

There is an important relationship between endogenous opioids and placebo. Some people do not respond to placebo by increasing endogenous opioid levels and they have hyperalgesic reactions to psychological distress. Hyperalgesia is more common in women than in men. It may explain why cold-induced pain is greater in women and why they respond more to naltrexone (Robinson *et al* 2005).

Men are better placebo responders than women (Aslaksen *et al* 2011). After placebo, pain unpleasantness was shown to be decreased in males but not females. This could have been caused by suppression or reduction of anticipatory stress.

Cicero *et al* (2012) showed that women suffer more from pain than men and have worse psychiatric outcomes in all age groups. It is important to use opioid therapy correctly in patients who are dependent on opioids because inappropriate treatment may worsen the pain and potentially exacerbate psychiatric problems.

Sexual hormones

Pain can be modulated by estrogens; estradiol being the most intensively studied estrogen. Estrogens are included in the pathophysiology of pain in migraine, temporomandibular pain and arthritis. Estrogens modulate the function of the nervous, immune, skeletal and cardiovascular systems. Estrogens can have both pronociceptive and anti-nociceptive effects depending on the type of pain and consequently they have both negative and positive effects (Brösen 2007).

Kumar *et al* (2010) compared the variation in responses during experimental pain in women with menstrual cycles and compared it with a one-month course of responses in men. Men showed no differences in responses to pain. Women reported higher pain sensitivity on the 14th day of their menstrual cycles. These cyclic changes were associated with increased fertility in a certain period of the menstrual cycle.

Bereiter & Okamoto (2011) demonstrated that estrogen was associated with the neurobiology of deep craniofacial pain. Estrogens act both peripherally and

centrally and affect the temporomandibular joint. He created a new term 'temporomandibular joint matrix,' which includes estrogen status.

Prof. Aloisi, from the University of Siena (Aloisi *et al* 2004), studied changes in pain perception in transsexuals taking sex hormones for development of the somatic characteristics associated with the opposite sex. 29% were converting from male to female and 61% from female to male. In male to female conversion, after estrogens and anti-androgens treatments, the most commonly reported pain was headache, breast and musculoskeletal pain. Women converting to men were given androgens (Aloisi *et al* 2011). Gender transformation induced pains of different origins. Some patients had more than one type of pain. In some patients, the pain was already present before the administration of hormones, but other types of pain appeared in association with testosterone.

CLINICAL FINDINGS

Genetic studies indicate not only the significance of sex differences, but also environmental effects. A predisposition to develop chronic pain in humans seems to be mainly associated with neuropathic pain. It includes trigeminal neuralgia, CRPS, phantom pain, back pain, menstrual pain, migraine, fibromyalgia, familial rectal pain syndrome and other peripheral neuropathies. In most cases these painful conditions appeared to be determined by multifactorial genetic and epigenetic factors.

Neuropathic pain

Complex regional pain syndrome (CRPS) is multifactorial and includes disorders of peripheral and autonomic nerves, the central nervous system, visceral system, connective tissues, and hormonal systems, all of which can induce psychological changes. It is impossible to find a single responsible system.

Bryce *et al* (2007) showed that the frequency of spinal cord injury (SCI) is relatively similar in men and women. Women with SCI have a higher prevalence of nociceptive pain than men and therefore the use of non-steroidal anti-inflammatory drugs (NSAID) was higher.

Pro-inflammatory cytokines facilitate neuropathic pain. They are up-regulated in peripheral nerves, dorsal root ganglia, and in some areas of the brain after peripheral nerve injuries. Direct application of exogenous inflammatory cytokines causes pain. Blockade of anti-inflammatory cytokine production reduces pain behaviors in many experimental models. Measurement of cytokine levels can identify patients at high risk of developing chronic pain associated with neuropathic causes such as peripheral neuropathy or postherpetic neuralgia. Anti-cytokine medication is important in the treatment of inflammatory pain, and it may also be used in certain neuropathies. Anti-cytokine treatment can stabilize and equalize the ratio between pro- and

anti-inflammatory cytokine levels in specific patients (Schäfers & Sommer 2007).

Fibromyalgia is a sex-linked disease (Lange *et al* 2010). Diagnosing fibromyalgia correctly is relatively difficult. In men, fibromyalgia is less frequent but, unlike in women, it is much easier to diagnose (Katz *et al* 2010). Previous experience is important regarding fibromyalgia outcomes. In patients undergoing multidisciplinary rehabilitation for pain, successful treatments, which improve physical and emotional function, often differ between the sexes (Hooten *et al* 2007).

Back pain

A large part of clinical research is devoted to back pain. We must take into account the fact that back pain in men has a psychological trigger more often than in women (Robinson *et al* 2004).

A paper by Fillingim *et al* (2003a), deals with the clinical characteristics of chronic back pain. In male patients with back pain, opioids cause affective distress, which was not present in female patients. On the other hand, women had higher pain intensity, which has been cited in a majority of publications. Also myofascicular pain syndrome, as a source of chronic back pain, was significantly more common in women.

Back pain, has also been studied from the point of view of emotive responses and the feelings of patients in pain. Assessors were nurses. Men expressed more pain than women but only when the nurse was looking at them. Addiction to pain often means an escape to pain (like escape to illness) that is significantly different in men and women (Watson & Shay 2010).

After the first injection of epidural steroids, for low back pain, men felt greater pain intensity and unpleasantness than women. After two weeks of treatment men had a greater reduction in pain, depression and disability than women. When the comparison was made after two months, gender differences were diminished (Inman *et al* 2004). Sex differences are common relative to shoulder pain (Kindler *et al* 2011).

Musculoskeletal disorders

Likewise, there are sex differences in the prevalence of musculoskeletal disorders (Budh *et al* 2003; Novicoff & Saleh 2011). Musculoskeletal pain is more common in women, but men have higher rates of disability. Low back pain is more common in men, while the entire spine is more often affected in women (Quiton & Greenspan 2007; Rollman & Lautenbacher 2001).

The study of musculoskeletal health in female dentists has shown that they are at higher risk of pain, from their work, than their male colleagues. It is caused by a specific pain syndrome, which is linked to back muscle imbalances. Women have a greater predisposition to musculoskeletal disorders and specifically to muscle pain. Women should go through preemptive ergonomic intervention and should be specifically trained to reduce the risk of pain (Diaz-Caballero *et al* 2010).

Musculoskeletal pain in the lower extremities, especially in the knee, is very widespread in the rural population of Tibet; Tibetans lead extremely hard lives which puts extraordinary demands on their knees (Hoy *et al* 2010). At younger ages, the incidence of leg pain is the same in both sexes; however in the older population, a higher incidence of pain has been described in women.

Muscle pain influences activity of the upper trapezius muscle in women but not in men. Women are more susceptible to muscle pain than men (Fala *et al* 2008). Women are also more sensitive to back pain; they are predisposed to specific anatomical conditions and also have reduced spine stability. When measuring the geometry of vertebrae, women have reduced vertebral sizes. Reduced stability of the spine also increases the potential for traumatic injuries (Valachi 2008).

Gender is a significant factor in the failure of total hip arthroplasty. Latteier *et al* (2011) presented a study involving 644 women and 719 men after arthroplasty. Arthroplasty revision was far more common in women than in men. High knee adduction, which was observed more often in women compared to men, can increase the risk for development of osteoarthritis and disorders of the anterior cruciate ligament.

Temporomandibular disorders

Women also have a higher prevalence of pain in the temporomandibular joint (Goncalves *et al* 2010). A higher prevalence of temporomandibular disorders (TMD) has been found in violinists who opened their mouth to stabilize the violin during playing (Rodríguez-Lozano *et al* 2010). Examination of the temporomandibular joint should be part of rheumatological examinations; such examinations could lead to better pain management (Alonso-Blanco *et al* 2012).

Rusanen and colleagues (2011) discussed the characteristics of TMD in association with typical facial pain, which occurs during biting, and oral health in patients with severe occlusions, a condition more common in women. Disorders of occlusion are directly related to oral health and quality of life. Patients with severe occlusion also have temporomandibular disorders and facial pain with decreased quality of oral health.

An American study, Plesh *et al* (2011), describes TMD and disorders of muscle tone along with other comorbid pains. Pain from temporomandibular joint disorders were usually associated with 2 or 3 other comorbid pains and only rarely occurred alone.

TMD pain is also related to deafness. TMD is far more common in women than in men. Mild forms of this disorder are associated with limitations in opening of the mouth, with ear abnormalities, and with normal audiograms. However, severe TMD involves hearing loss of high and low frequencies (Kitsoulis *et al* 2011). A lower prevalence of TMD in men has been explained based on the protective effects of testosterone (Fisher *et al* 2007).

Pain measurement in patients with painful diabetic peripheral neuropathy has clinical significance for accurate diagnosis of the disease. The intensity of trigeminal pain in women was associated with lower levels of glycated hemoglobin (Petriconis *et al* 2010). Orofacial pain was more common in women than in men, with higher pain thresholds correlated with higher glucose levels and glycated hemoglobin (Arap *et al* 2010).

Dental pain

Sex differences relative to dental pain and fear of dental pain can be caused by psychogenic, psychological and psychosomatic factors. Although a single application of both pentazocine and naloxone induced greater analgesia than placebo, ontological analgesia was greater when pentazocine and naloxone were administered together. Analgesia was greater in women than in men for this type of pain; however pentazocine alone had the opposite effect (Ryan *et al* 2008).

Ergonomic factors cause pain in dentists. Their job puts long term stress on overloaded skeletal muscles (Doyal & Naidoo 2010). Dentists suffer from muscle pain in the back, neck, shoulders and hands. Therefore, it is necessary to devise an occupational health program that seeks to modify their lifestyle; this is especially true for women (Diaz-Caballero *et al* 2010).

Headache

Headache is another pain state which is more common in women than in men. Migraine has the highest incidence at about age 40 and then decreases, regardless of race or ethnicity (Peterlin *et al* 2011). Frequency of migraine attacks is very dependent on hormonal cycles, but psychosocial factors also play an important role. Epidemiological findings show that women have a higher degree of incapacity, relative to work, and more psychiatric comorbidities associated with headaches than men.

Hunt *et al* (2011) studied the association between gender and frequency of medical consultations for back pain and headaches. Women consulted more often for general symptoms (e.g. headache and back pain) than men.

Chest pain

Post-sternotomic chronic pain is a very intense sternal pain syndrome. It is often accompanied by headaches, neck pain, back pain and pain in the upper extremities. We do not know the exact cause of this type of pain, but it is more common in women than in men (van Leersum *et al* 2010).

According to the study "Monika" (Kirchberger *et al* 2011), women suffer far more pain on the left side than with the other syndromes. Gender differences were described for chest pain, pain in the right shoulder or synkopias but no differences were found relative to acute myocardial infarction, from the point of view of pain intensity.

Abdominal and pelvic pain

Results of pain treatment in emergency department patients with acute abdominal pain indicate that women have less sensitivity to opioids and therefore oligoanalgesia is a problem; opioids should be used as part of a combination therapy, as shown experimentally (Banz *et al* 2010).

Irritable bowel syndrome (IBS) is also a gender and lifestyle dependent disease. Less important, secondary factors, include environmental factors, psychosocial stressors, gastrointestinal infections, antibiotics, and food (Spiller 2011).

Pelvic pain can be very intense. Since this type of pain differs in men and women, it must be treated differently with respect to reduced sensitivity to opioid therapy in women (Savoye-Collet *et al* 2010). Pelvic disorders, particularly in the posterior pelvic region are sex dependent. Defecography has shown different abnormalities in men and women, mainly in the rectocele and enterocele. Perineal disorders were observed far less frequently in men than in women; in women perineal protrusions were more frequent (Moise *et al* 2007).

Sex differences predict quality of life in patients with cancer pain. Sex is an accessory factor in the characteristics of quality of life, but the differences between individual patients are larger than the differences between sexes.

PSYCHOSOCIAL FACTORS

Pain is influenced by psychosocial factors which represent an integral part of cultural position, race and ethnicity; however, it may be changed by actual mood and especially by psychiatric conditions such as depression. Strong interactions exist between ethnicity, religiosity, and gender and pain anticipation.

Graham *et al* (2011) tried to ascertain which health conditions make people most unhappy. They found that anxiety and pain had a stronger impact than physical conditions, since people adapt better to single specific stresses than to complex uncertain stresses. The impact of negative emotions is much broader than that of positive emotions.

Women are far more self-critical. Self-criticism interacts with morbidity, including depression, and represents an important factor of affective pain. Depression also increases in parallel with increasing self-criticism.

Women are more prone to catastrophization than men (Edwards *et al* 2003). The impact of catastrophization on pain is expressed more in clinical pain than in experimental pain.

Darnall *et al* (2010) published a pilot study on the development of inflammatory responses in people with chronic pain. Inflammatory responses that coincided with negative emotional experiences were more intense and of longer duration in women with chronic pain than in men. In the first phase of pain, the duration of pain

symptoms depends on cytokine responses which represent critical factors for the future development of pain.

Fillingim *et al* (2003b) described perception of chronic pain to be dependent on patient marital status. Men who lived alone had increased perception of pain and impaired quality of life; while women living and feeling alone, had lower pain tolerance, they also reported that pain interfered more with daily tasks such as walking or lifting. Single women also used more opioid medications. Men and women living alone had higher pain scores during testing, something which should be taken into account during pain management.

Various chronic pain conditions can be more dangerous for women than for men and psychological stress, which involves sympathetic activation, is the cause (Vierck *et al* 2008).

Haskell *et al* (2010) described gender differences in the incidence of depression in post-traumatic stress syndrome, pain, obesity and sexual trauma in USA veterans who had fought in Iraq and Afghanistan. The most important sex differences were found associated with a positive screening for MST (military sexual trauma), depression, obesity and post-traumatic stress disorder. These findings are valuable with regard to pain perception.

Robinson *et al* (2005) studied the effect of gender and fear on temporal summation of pain. Summation of pain is a phenomenon that occurs in both men and women. After repeated thermal stimulation, women felt greater pain intensity compared to men. Temporal summation is affected by anxiety and social learning, which determines the role of men and women regarding attitudes toward pain.

Jensen *et al* (2011) showed that fear was a significant predictor in women with back pain and that previous back pain may serve as a predictor for monitoring pain in the upper limbs. Previous pain intensity seems to be the main factor that influences present acute pain and prescription of analgesic effectiveness (Dao & LeResche 2000; LeResche 2011).

Ethnicity

Women have a different biological mechanism for pain and ethnic subgroups have different mechanisms for perception and response to pain (Jackson *et al* 2002).

Race and sex play an important role in low back pain. Pain is reported to be more intense in white and Hispanic women throughout life; it is also more intense for non-white men in their sixties. Occurrence of neck pain increases until age 60 and is more common among younger Hispanic women; in later life this pain becomes more common in men, with the highest frequency in the non-white population (Green & Hart-Johnson 2010).

An interesting study, conducted by neurologists and algologists from Toronto, showed that in addition to gender, ethnicity was also an important factor. Several U.S. publications show different results when tested for

pain; differences were found in white Americans and African-Americans living in the same social and geographical environment. African-Americans felt more pain than white Americans, which was especially true in women. It is necessary to provide further studies before an accurate explanation of these differences can be offered (Campbell *et al* 2008; Hastie *et al* 2004; Sato *et al* 2011).

RESEARCH IN ANIMAL MODELS OF PAIN

Responses to prolonged painful thermal stimulations have been tested in Long Evans and Sprague-Dawley rat strains. In female rats, cold nociceptive stimulation was more aversive than hot stimulation whereas opposite results were found in male rats (Alabas *et al* 2012b; Filingim *et al* 1999; Kakeda & Ishikawa 2011).

Stress during the prenatal developmental period can also change sensitivity to pain. When pregnant rats had formalin injected into their paw, postnatal testing of their offspring showed that prenatally stressed male rats were more sensitive to pain than female rats (La Prairie & Murphy 2007).

On the other hand, female rats were more sensitive to inflammatory processes. Females, damaged by neonatal hypoxia and undernutrition, developed in adulthood, greater inflammatory hyperalgesia after intraplantar injection of carrageenin or Freund's adjuvant compared to equally injured males.

Males were found to be more sensitive to morphine than females and females were found to be more sensitive to pain and less sensitive to opioids, therefore it is important to combine two analgesics such as gabapentin and tramadol (Gaumont *et al* 2007). Antinociceptive effects of tramadol and gabapentin were investigated in mice using the tail-flick test (tramadol was administered at a dose of 60 mg/kg, gabapentin at a dose of 75 mg/kg). ED₅₀ for antinociceptive effects in tramadol were lower in males than in females, females were less sensitive to this drug. Conversely, gabapentin had only limited antinociceptive effects in both males and females. When both drugs were combined, no sex differences were observed (Dai *et al* 2008; Gioiosa *et al* 2008).

Morphine preferentially activates the pathway between periaqueductal gray matter and the rostral ventromedial medulla (RVM). Activation of this axis is greater in males than in females and this is probably the cause of morphine induced antinociception that is frequently observed in males. Periaqueductal gray matter in the midbrain and its descending projections to the RVM constitute a basic circuit for opioid analgesia. The effect is also sexually dimorphic (Popescu *et al* 2010; Loyd *et al* 2007).

The antinociceptive effects of morphine are stronger in rodent males than females. This was demonstrated using rats, when animals of both sexes had morphine injected into the ventrolateral periaqueductal gray matter. Male rats were compared with females during

their estrous cycle; the observed antinociceptive effects were greater in males than in females during proestrus, followed by estrus and metestrus (Craft 2007).

Similar results were observed in the sensitivity of mice to morphine. Nociception was tested using the hot plate test and gonadal males (genotype XX and XY) and in gonadal females (genotype XX and XY). Males were more sensitive to morphine than females and the sensitivity was always Y chromosome dependent. Therefore, genes localized on X or Y chromosomes could be responsible for sexual dimorphism in pain perception and analgesia. Hormones affect sensitivity to opioids far less than expected (Gioiosa *et al* 2008).

Modulation of morphine analgesia, by estrogen, in visceral pain in female rats can be mediated by supraspinal and peripheral factors. Although females are less sensitive to morphine-induced analgesia than males; after ovariectomy or estrogen substitution, females have stronger responses to morphine than males. In intact females, estrogen is one of the key factors that contribute to sex differentiation of μ opioid analgesia (Ji *et al* 2011).

Cataldo *et al* (2010) studied the effect of ventromedial and medial preoptic hypothalamic lesions induced by ibotenic acid. These nuclei are involved in morphine-induced analgesia in female rats but not in males. In intact females, ventromedial hypothalamic nuclei and medial preoptic nuclei respond with tonic inhibition that originates from endogenous pain inhibitory circuitry. This is related to levels of circulating sex hormones, which has been demonstrated in ovariectomized rats. Excitotoxic destruction of estrogen receptors weakens the analgesic response to systemic administration of morphine.

There are sex differences in activity and modulation of N-methyl-D-aspartate receptors (NMDAR) in dorsal root ganglia (DRG). Beta estradiol has been shown to modulate NMDA receptor activity in DRG neurons. Electrical currents of NMDA receptors in these neurons were three times longer in females than in males (Butkevich *et al* 2007a,b).

Endothelin 1 is a vasoactive peptide which is released into the systemic circulation after stress and pain caused by cold. It is formed locally in tissues after injury or disease. Endothelin 1 is also produced during spontaneous nociceptive behavior and after mechanically induced allodynia. Release of endogenous endothelin is greater in younger compared to older organisms. Endothelin 1 induces mechanical allodynia in all age groups but is produced more in young females (McKelvy *et al* 2007).

Modulation of visceral pain is dependent on BDNF (brain-derived neurotrophic factor) that facilitates visceral pain in female rats, but has the opposite effect in males. With regard to clinical pain management there is a significant difference (Li *et al* 2010a).

Neuregulin I was discovered in the spinal cord. It is a growth factor and pro-nociceptive cytokine that is modulated by progesterone in the spinal cord. In

females, neuregulin I is one of many factors responsible for central sensitization during ongoing pain. Thus progesterone-dependent regulation of neuronal or glial neuregulin production in females could be the cause of sexual differentiation in nociception and increased pain perception (LaCroix-Fralish *et al* 2008).

Belinger *et al* (2007) showed that capsaicin-sensitive neurons in inflammatory TMD produce different nociceptive responses in male and female rats. Capsaicin-sensitive neurons are partially responsible for the transmission of acute nociceptive pain. As nociception in the inflamed region is gender specific, females are more susceptible to the development of this effect.

Genetic studies show which genes are responsible for sexual dimorphism in pain perception. Genes expressing neuregulin I and its high affinity receptor RB4, as well as genes for tachykinin 1 and metabotropic glutamate receptor 6, have been shown to be specific and are increasingly up-regulated in damaged L5 roots in females (LaCroix-Fralish *et al* 2008).

In animal research, both gender and strain play important roles. Just as in humans, mice and rats also demonstrate psychosocial effects (Edwards *et al* 2003; Paulson *et al* 1998).

CONCLUSION

From the above survey it can be concluded that pain perception is different in males and females. Differences have been found in the pathophysiology, pathogenesis and clinical manifestations of diseases. These differences are important with regard to treatment, which should be gender-specific. These fundamental differences also relate to ontogenetic factors. Childhood, adulthood, and elderly populations of males and females respond differently to pain and its treatment, therefore this should be taken into account during clinical pain management.

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