The Role of Sex Hormones in Females Greater Sensitivity to Pain

By

Michael Gomez

Supervisor - Dr John Harris

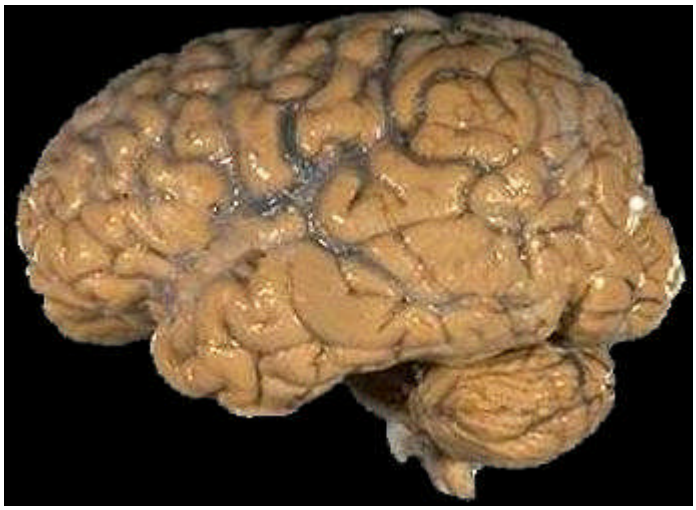

Figure 1. Exteraal side view of a preserved human brain
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Introduction

Over the past ten years, it has become increasingly evident that the experience of pain differs between the genders. Women are more likely to suffer from both acute and chronic pain and to use more pain-relieving medications (Craft, 2007).

One hypothesis for these differences considers the presence or absence of specific sex hormones. These are mainly steroids which control sexual development; the oestrogens in females and testosterone in males. It may be that they have other roles because their receptors are located throughout the body (Solomon *et al*., 2005).

Migraines, temporomandibular disorders (painful conditions involving the jaw) and arthritis are just a handful of chronic pain conditions which are more prevalent in women. Several studies have linked oestrogen to their development and severity. Unfortunately, it cannot be concluded that oestrogen is the cause of these painful conditions. The scientific data varies considerably, from high oestrogen levels preventing pain by acting in the spinal cord, to oestrogen being synthesised and causing pain within a joint. This study has taken a close look at the effects of oestrogen on migraine,jaw pain and arthritis to establish whether sex hormones really do play a role in pain modulation.

The Physiology of Pain

It is said that the ability to experience pain is one of the most precious gifts bestowed on us by Mother Nature. Without the perception of pain damage and disease cannot be assessed by the individual and avoided or treated. To understand how oestrogens may affect pain it is important to understand the process by which a person feels pain. The pain pathway starts at pain receptors, also known as nociceptors. These are wide branches of fibres which penetrate various levels of the skin. When the skin experiences painful stimuli nociceptors are activated and initiate a signal which is passed along nerves to the dorsal horn of the spinal cord.

Nociceptors come in two main forms. The first type are known as Aδ fibres and have a conduction velocity of 3 – 30 ms^{-1}. They are responsible for the initial pain felt after injury, also known as first pain. The second type of nociceptors are C fibres. These have a much slower conduction velocity of less than 2 ms^{-1} and are responsible for the duller,

longer-lasting feeling felt after injury. This is known as second pain (Bear *et al*., 2007).

As mentioned earlier, the nerve fibres terminate in the dorsal horn of the spinal cord, specifically in an area known as the *substantia gelatinosa*. This has been summarised in figure 3. The signal is then propagated onto ascending nerve fibres by a neurotransmitter. The most common neurotransmitter is glutamate, an excitatory amino acid.

After synapsing in the *substantia gelatinosa*, the signal then continues along ascending pathways to the brain. One such example is the spinothalamic pathway; discovered to be associated with pain over one-hundred years ago. Lesions of this pathway result in the loss of sensation and ability to feel noxious stimuli (Dostrovsky *et al*., 2006). These ascending pathways are responsible for the conscious recognition of pain (I.e. saying 'Ouch') along with pain behaviour (I.e. moving away from the danger).
Figure 3 also shows a red nerve fibre leaving the ventral horn of the spinal cord. In terms of pain, these efferent fibres result in unconscious reflexes or survival instincts. An example of this would be the quick withdrawal of the hand when touching something hot or the speedy withdrawal of the foot after stepping on a pin.

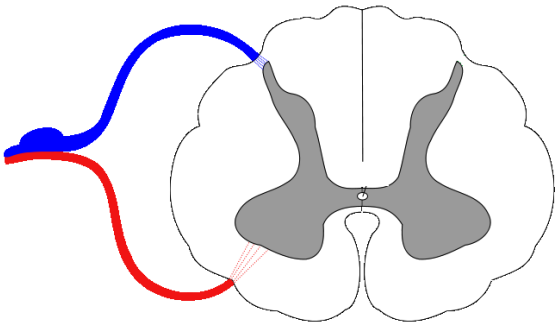

Figure 3. Diagrammatic representation of a horizontal section of the spinal cord. The blue line represents a C fibre entering the dorsal horn. The red line represents a motor fibre leaving the ventral horn of the spinal cord (adapted from http://commons.wikimedia.org).

The Sex Hormones

Sex hormones are cholesterol-derived steroid hormones secreted primarily by the male and female gonads. Their secretions are tightly controlled by the hypothalamo-pituitary axis.
Oestrogen has several functions including development and maintenance of the uterus, mammary gland maturation, an effect on mood and it also promotes bone maturation (Murray *et al*., 1996).
Oestrogens are formed from androgens via a series of complex hydroxylation steps. The primary oestrogen is 17β-oestradiol, however oestrone and oestriol are also formed. After production, oestrogens are transported in the blood bound to a protein known as sex hormone-binding globulin or SHBG.

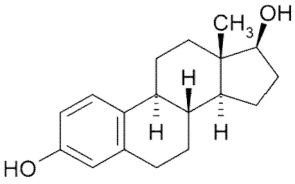

Figure 4. The structure of 17β-oestradiol (taken from http://commons.wikimedia.org).

The oestrogen receptor (known as ER) belongs to a family of intracellular steroid hormone receptors. It has two forms; ER-α and ER-β, both of which act as transcription factors that are able to regulate several genes. In relation to pain, tracing techniques have been used to show that the ER is located in lamina I and II of the spinal dorsal horn; these areas are strongly associated with pain transduction.

Testosterone is the main sex hormone produced in males. It has several functions including spermatogenesis (process of sperm production), growth, aggression and cardiovascular health.
It is synthesised in a five-step reaction starting with cholesterol. Like oestrogen, testosterone is transported whilst bound to SHBG.

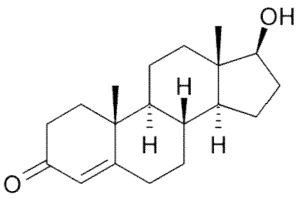

Figure 5. The structure of Testosterone (taken from http://commons.wikimedia.org).

The testosterone receptor (also known as AR) is very similar to the ER in terms of structure and binding. It is located throughout the body including the central nervous system however studies have shown its role is pain modulation is not as significant as that of the oestrogens (Murray *et al*., 1996).

Migraines

A migraine can be defined as a chronic neurological disorder with the main symptom being pain around the skull. Roughly 10% of the population are affected by migraines and this ratio is skewed towards females. The exact physiology

of a migraine is unknown however it is believed to start in an area of the brain stem known as the periaqueductal gray. This area is of interest for two reasons; firstly, it is a known area associated with pain and antinociception (reduced sensitivity to pain) and secondly, this area has a high density of the ER.

Evidence has been gathered to support the hypothesis that oestrogens play a role in the onset of migraines. These have been summarised below:

- Migraines are approximately three times more common in women than men.
- Oestrogens are able to pass the blood-brain barrier meaning they can act within the brain.
- Sex differences in migraines emerge at puberty (as oestrogen levels rise) and decline after menopause (as oestrogen levels fall).
- Up to 50% of female migraines occur within ±2 days of menstruation.
- Almost 80% of pregnant migraine sufferers experience complete relief of migraines during pregnancy. And nearly all of them experience a return of symptoms after the birth.

Figure 6. A young girl rubbing her temples. A classic sign of a migraine (taken from http://commons.wikimedia.org).

Although a lot of evidence exists to strengthen the theory that oestrogens are involved in migraines, no single mechanism has been proposed. The most promising idea was put forward by Welch *et al.* (2006). This revolves around the decreasing levels of oestrogen experienced just before ovulation. Low oestrogen increases the excitability of neurones both directly and indirectly via neuropeptides, leading to pain and other associated disabling aspects of migraine.

Temporomandibular Disorders

Temporomandibular disorders or TMDs refers to a group of painful conditions involving the muscles of the jaw; specifically the temporomandibular joint (or TMJ). There are many known risk factors for TMDs, and in general, no single risk factor is of overwhelming importance. Examples of these factors include genetic aspects, trauma, teeth misalignment and sex hormones.

TMDs are approximately twice as common and more severe in women compared to men. Similar to migraines, their onset is typically after puberty and then declining postmenopausally. To analyse if oestrogen does play a role in facial pain, Flake *et al.* (2005) looked at TMJ nerve activity in rats which have had their ovaries removed and thus no longer produce high concentrations of oestrogen. The rats were separated into two groups; one group treated with oestrogens and one without. An injection of Complete Freund's Adjuvant (which is known to induce inflammation thus increasing nerve activity) was administered directly into the TMJ of each rat and then nerve activity was measured. A diagrammatic representation of the results can be seen below.

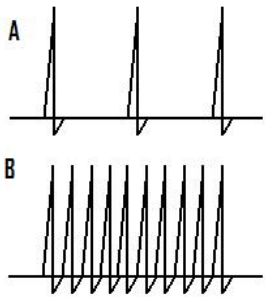

Figure 7. TMJ activity after injections of Complete Freund's Adjuvant. Activity is increased in group B, those treated with oestrogen (drawn using Microsoft Paint).

Each peak represents activity within the joint and the results showed that the rats treated with oestrogen experienced a much higher level of activity compared to those rats whose oestrogen levels had declined after being ovariectomised. These results help formulate a hypothesis explaining why women experience more severe TMDs compared to men.

Arthritis

Arthritis is any condition of the joints which is associated with inflammation or structural change. Although several different types of arthritis exist, the two most common forms are osteoarthritis (OA) and rheumatoid arthritis (RA). It is estimated that over forty-two million people in the world suffer from arthritis in one form or another and symptoms range from minor aches and pains to life-threatening conditions. Arthritis can be influenced by several factors including genetic aspects, obesity, trauma, smoking and sex hormones. The effects of oestrogens on arthritis have been studied extensively in both animal models and human patients and several theories exist which help explain why arthritis is more prominent in women.

As previously mentioned, a lot of studies have

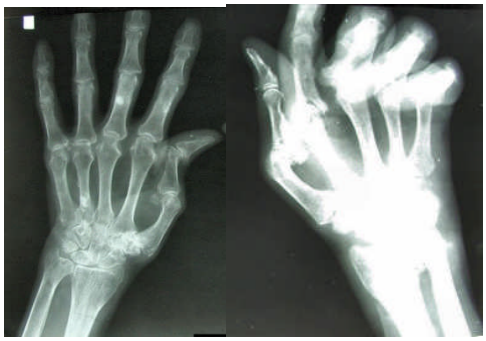

Figure 8. X-rays from two different patients. The left hand is a healthy patient and the right hand is a patient suffering from rheumatoid arthritis (taken from http://commons.wikimedia.org).

been undertaken on oestrogenic modulation of arthritis and some of these studies have been summarised below:

- Women over fifty are more likely to develop arthritis compared to men over fifty.
- Joints affected by arthritis have higher levels of oestrogen within them compared to unaffected joints.
- Arthritis sufferers report less pain during pregnancy.
- Blocking the ER with an antagonist results in an earlier onset of arthritic symptoms.
- Induced arthritis in ovariectomised mice is more severe when compared to non-ovariectomised mice.
- Oestrogen treatment in ovariectomised mice has an anti-arthritic effect.

Oestrogen exerts a protective role when levels are high however as levels decline (either naturally or due to experimental procedure) the risk and severity of arthritis increases (Straub, 2007). Although it is clear that oestrogen plays a role in arthritis, no mechanism is known. The ER is located within joints suggesting oestrogen has a local effect however there are several other factors which may also play a role.

Conclusion

The aim of this project was to discuss the role of sex hormones in the differences in pain perception found between males and females. Several studies have implicated oestrogens as a key modulator of pain in adults. It is notably associated with the three pain syndromes discussed above via various different mechanisms however no specific conclusion can be drawn. In fact, it is safer to assume that oestrogen is just one of several factors involved in complex pain modulation. As oestrogen can both cause and relieve pain, further knowledge of these mechanisms may help in the prevention and treatment of pain in both males and females.

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Author Profile

"Michael is 22 years old and studied in the School of Biosciences graduating in 2009 with a first class degree, BSc (Hons) Animal Science. After taking a year out to travel, he is starting a graduate medicine programme with the aim of becoming a neurosurgeon."