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REVIEW

INSIGHTS INTO THE MECHANISMS AND THE EMERGENCE OF SEX-DIFFERENCES IN PAIN

MEGGANE MELCHIOR,[a] PIERRICK POISBEAU,[a] ISABELLE GAUMOND[b] AND SERGE MARCHAND[b]*

[a] *Centre National de la Recherche Scientifique and University of Strasbourg, Institute for Cellular and Integrative Neuroscience (INCI), F-67084 Strasbourg, France*

[b] *Centre de recherche du CHUS and Département de chirurgie, Faculté de médecine de l'université de Sherbrooke, Québec, Canada*

Abstract—Recent studies describe sex and gender as critical factors conditioning the experience of pain and the strategies to respond to it. It is now clear that men and women have different physiological and behavioral responses to pain. Some pathological pain states are also highly sex-specific. This clinical observation has been often verified with animal studies which helped to decipher the mechanisms underlying the observed female hyper-reactivity and hyper-sensitivity to pain states. The role of gonadal hormones in the modulation of pain responses has been a straightforward hypothesis but, if pertinent in many cases, cannot fully account for this complex sensation, which includes an important cognitive component. Clinical and fundamental data are reviewed here with a special emphasis on possible developmental processes giving rise to sex-differences in pain processing.

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Key words: pain, nociception, sex hormones, gender, sex, development.

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INTRODUCTION

Women and men do not experience pain equally. Women perceive painful stimuli as more intense than men and are overrepresented in the majority of clinical pain conditions (Mogil, 2012). Interestingly, the same is true in animals, females having a lower pain threshold than males, supporting the implication of biological differences (Craft et al., 2004).

A great interest in the problematic of sex-differences in pain responses and pain processing has emerged in recent years. The number of dedicated clinical and animal studies has widely increased and supports the idea that pain seems to be processed differentially in men and women. Animal studies have been a huge help in deciphering potential mechanisms linked to the differences observed, raising the question of inherent anatomical differences between the two populations, and of the role of gonadal hormones in the modulation of pain responses.

Pain is a complex phenomenon relying on intricate excitatory and inhibitory psychophysiological mechanisms. Chronic pain frequently results in an

*Corresponding author. Address: Department of Surgery, Université de Sherbrooke, Centre de recherche du CHUS, 3001-12e Avenue Nord, Sherbrooke (Québec) J1H 5N4, Canada. Tel: +1-819-820-6868x15889.
E-mail address: serge.marchand@usherbrooke.ca (S. Marchand).

Abbreviations: ANS, autonomic nervous system; BP, blood pressure; CFA, Complete Freund's adjuvant; DRG, dorsal root ganglion; fMRI, functional magnetic resonance imaging; FSH, Follicle-stimulating hormone; GABA, gamma-Aminobutyric acid; KOR, kappa-opioid receptor; LH, Luteinizing hormone; LPS, Lipopolysaccharide; MK801, dizocilpine; MOR, mu-opioid receptor; NICU, neonatal intensive care unit; NMDA, N-methyl-D-aspartate; PAG, periaqueductal gray matter; PBn, parabrachial nucleus; PET, positron emission tomography; RVM, rostro-ventral medulla; SIA, stress induced analgesia; TLR4, Toll Like Receptor 4.

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excessive recruitment of excitatory mechanisms often referred to as peripheral and central sensitization. Excitation is often further amplified by a reduced efficacy of inhibitory controls exerted by local interneuronal networks or by supraspinal axonal projections (e.g. Conditioned Pain Modulation – CPM) (Yarnitsky et al., 2014; Todd, 2015). Recent studies have highlighted that patients exhibiting an increased sensitization by temporal summation versus a deficit of CPM are expected to respond positively to different classes of drugs (Yarnitsky et al., 2012; Olesen et al., 2013) .

Beside the physiological responses after recruitment of somatic and autonomic systems, the role of cognitive and emotional processes is of utmost importance. In classical views, the term sex refers to a person's biological status as defined by sex chromosomes, gonads, internal reproductive organs and external genitalia. Gender refers to the attitudes, feelings, and behaviors that a given culture associate with a person's biological sex (American Psychological Association, 2012). In this review, we will use the term sex-specificities as a generic term, also covering any gender-specific differences in pain processing and expression. We will put some emphasis on the developmental origins of sex-differences in pain and provide some clinical and experimental observations supporting the differential pain responses during the development from childhood to adulthood in both animal models and human. The implication of the environment linked to early life events which could differentially imprint and alter pain processing in a long-term manner in a sex-specific manner will also be discussed.

PERCEPTION AND REACTIVITY TO PAIN

Experimental pain

Numerous clinical studies have highlighted differences in the perception of pain between men and women. Stimulating different tissues like skin, muscles or even visceral sites using electrical, thermal or mechanical stimuli can be used to assess the pain response. These experiments allow measuring pain threshold (when the subject describes the first sensation of pain), pain tolerance (how long the subject can support pain before it becomes unbearable) or the efficacy of endogenous descending controls of pain using dynamic models of experimental pain. Evidence from experimental pain studies report that women display higher pain responses for both electrical and thermal stimuli (Fillingim et al., 2009), but the results seem, however, highly dependent on the modality of pain stimulation (Riley et al., 1998; Racine et al., 2012).

For example, women exhibit lower threshold and tolerance of pressure pain when cutaneous territories are stimulated with pressure algometers or Von Frey filaments (Racine et al., 2012). Suprathreshold mechanical stimulation induces greater reported pain sensitivity (i.e. hyperalgesia) in women compared to men, and an associated greater autonomic response as measured by pupil dilation (Ellermeier and Westphal, 1995). However, using a dynamic model of experimental pain (temporal summation of pain using a train of 10 mechanical stimulation of the finger by a sharp probe), Sarlani and Greenspan describe a higher pain rating by women of the 5th and 10th stimulation (Sarlani and Greenspan, 2002), and a greater unpleasantness together with painful after sensations at the end of the train of stimulation (Sarlani et al., 2004). However, this difference in pain ratings could not be reproduced in another independent study stimulating the tibialis anterior (Nie et al., 2005).

Most studies tested pain responses to thermal stimulation after immersion in cold or hot water. Although few studies failed to describe any sex-differences, a large amount of data conclude that women display lower pain thresholds and pain tolerance compared to men, as seen in a recent meta-analysis (Racine et al., 2012).

On the contrary, studies assessing ischemic pain sensitivity were inconclusive regarding sex-specificities in thresholds or tolerance to ischemic pain (Bragdon et al., 2002; Racine et al., 2012).

Brain imaging

Results from imaging studies are sometimes inconclusive, but clearly indicate that nociceptive information could be processed differently by the pain matrix in men and women. As studied by functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), several brain regions activated by a painful stimulus have comparable activities in men and women, among which the premotor cortex, primary motor (M1) and somatosensory (S1) cortices and the cerebellum (Paulson et al., 1998). A sex-specific activation of few brain regions is also reported using nociceptive stimuli adjusted for individual pain perception. For example, Derbyshire and colleagues used a calibrated thermal stimulus to induce the same pain response in both men and women, but a different pattern for cortical activation (Derbyshire et al., 2002). In men, the thermal stimulus induced activation of the parietal cortex bilaterally, the contralateral secondary somatosensory cortex, the prefrontal cortex and the insula, while the ipsilateral perigenual and ventral cingulate cortex were preferentially activated in women. Using the same stimulation paradigm, another research team reported a sex-specific activation of the prefrontal cortex contralateral to the stimulation in male and ipsilateral to the stimulation in females (Paulson et al., 1998). This observation, if confirmed, suggests a possible sex-specific lateralization in pain processing and particularly with regard to the emotional dimension of pain. The same study also demonstrated a greater activation of the contralateral thalamus and anterior insula in women, who described the stimulus as more painful than men. Differential brain activation has also been detected using electrical stimulation of the finger, as indicated by a greater activation of the contralateral medial prefrontal cortex in women and a greater activation of the ipsilateral posterior insular cortex in men (Straube et al., 2009). On the contrary, Moulton and colleagues, using fMRI and BOLD signal, demonstrated a greater deactivation of the primary