Understanding Sex Differences in Pain

In a recent study by Jeffrey Mogil et al, a male-specific pain-memory mechanism was found. It has been suggested that the chronification of pain is heavily dependent on pain memories. (Shiers) Chronic pain is of particular interest to some researchers as it seems to express more in females than males (Mogil). Chronic pain has been induced in studies before as conditioned hypersensitivity to study a long-lasting pain response. (Shiers)

In this study by Mogil, through conditioned hypersensitivity to a particular researcher and location, it was found that pain memories are experienced more strongly by males than females (Shiers). The importance of this finding can be seen through looking at studies and opinions about how to study and address the apparent sex differences in pain throughout the last few years.

AROUND 2010

In the scientific community, the study of the biological sex-specific pain mechanisms was not always considered important. This is somewhat shocking since, for example, we have known that there are biological reasons for pain's impacts on human capabilities. For example, a study in 2010 revealed that pain can result in decision-making deficits through the correlated BLA hyperactivity (Ji).

A discussion paper by Manson also published in 2010 promotes this idea that studying pain differently between the sexes is not necessarily important. He argued that psychological and social variables may more powerfully impact the perceived sex differences in the experience of pain than do biological variables (Manson).

One study that supports this idea concerns social pain. Some evidence suggests that it is very biologically similar to physical pain, one piece of evidence being that people who took acetaminophen over 3 weeks reported reduced amounts of emotional pain in response to social rejection (Vangelisti). The results of the study showed that men who took the medication actually felt more social pain than men who took the placebo pill; the opposite was true for the female participants. An explanation for this that the authors presented was related to the societal expectations for men to be non-emotional, suggesting that men may actually feel more pain after taking the pill because they are more willing to convey it (Vangelisti).

However, a discussion-paper by Jeffrey Mogil in 2012 addressed these multiple explanations and approaches to the explanation for why pain seems to express differently between the sexes. Mogil explained that although we still don't know exactly why there are drastically more females who experience chronic pain than males, we should not risk over-generalizing about what we find in males (Mogil). This often happens because many studies on pain are conducted primarily on male mice because of the complexities of also dealing with a female's cycle (Mapplebeck). There has been a need to study the mechanisms of female and male pain

differently, not simply explaining sex discrepancies with social reasons or generalizing studies done on males to both sexes.

GOING FORWARD TO 2015-16

Luckily, there were people that agreed and research continued on attempting to isolate what mechanism or mechanisms may be involved differentially with pain in males and females. There are two studies from 2015 and 2016 that used allodynia, a condition that can be induced in the test mice such that neutral, non-painful stimuli now cause pain.

The results from this study show that there are biological explanations behind the different sex experiences of pain. In Nasir et al's study in 2016, they induced this condition in mice while altering the expression of a specific gene, PKMzeta. They found that PKMzeta had a larger impact on allodynia in males more than in females (Nasir). The 2015 study found that allodynia in females was impacted most from T cells, cells in the immune system, whereas in males the pain promotion is from microglia, cells in the central nervous system. Furthermore, this sex-difference depend on testosterone levels (Brings).

From these studies we can see that while the work from around 2010 likely is correct in some ways, there also is an importance in studying the biological underlyings of pain from a sex-specific standpoint. This recent finding of male-specific pain-memory takes us a step further as we learn more about pain memory. This is particularly notable since pain-memory is theorized to be connected to the chronification of pain (Shiers), which seems to impact females more than males (Mogil). This sex-difference and sex-discrepancy are not largely reflected in much of the research on pain, which often use males to represent both sexes (Mapplebeck), further making this identification of male-specific pain memory that more significant.

IMPLICATIONS

Mogil's study on pain memories give us an increased understanding of and is additional

evidence that there does exist biologic pain differences between the sexes. Though that doesn't rule out other factors such as societal expectations, this finding should change how we approach treating chronic pain and pain memory in females versus males. Because of the complexities of pain, we must continue to research the different mechanisms behind pain for both sexes with a goal of using this knowledge to better treat pain in both men and women (Manson).

Mogil's study actually takes us a step closer to this, having specifically found that both a *zeta inhibitory peptide* (ZIP) and an *atypical protein kinase C* (aPKC) inhibitor interrupt the male-specific pain memory, also then likely stopping the chronification of pain (Shiers). This is directly exciting for the prospect of treating chronic pain in males. It is indirectly exciting in regards to females since if a system like this exists for males, there's likely one for females as well. This is especially exciting in light of the male-biases that have existed in the research of

pain in the past, and we will hopefully soon find a similar system for females. As Mogil explained in a paper he published in 2012, “given that women with chronic pain greatly outnumber men, to ignore female-specific pain biology is to do a great ethical disservice to the majority of people with this condition” (5, 864). This study finding the male-specific pain memory is encouraging since it suggests that the scientific community is on its way towards figuring out how to best treat pain in males and in females.

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