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The Influence of Sex Hormones on Osteoarthritis Pain Perception in Mice

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Abstract

Introduction: Despite the higher prevalence of osteoarthritis (OA) in women, animal studies are primarily performed in young male mice. There is evidence that cartilage degeneration is more severe in male mice which can be explained by the protective effect of estrogen against OA in females. This aligns with the onset of OA often occurring after menopause in women. This proposed study will assess the potential limitations of using male mice by evaluating the differences in OA pain perception between male and female mouse models, and the role of sex hormones.

Methods: A total of 96 mice will be used, split into four groups (n = 12) within their sex: sham, sham + ovariectomized (OVX)/orchiectomized (ORX), destabilization of the medial meniscus (DMM), and DMM + OVX/ORX. Half of the female (n = 24) and male mice (n = 24) will then receive DMM surgery to induce post-traumatic OA. Electronic von Frey (EvF) will be used to measure mechanical allodynia and Pressure Application Measurement (PAM) will assess knee hyperalgesia. Open field testing (OFT) will evaluate locomotor and behavioural activity. Twelve weeks after DMM, all mice will be sacrificed, and knee histological sections will be taken to assess for OA damage using the OARSI and synovial scoring system.

Anticipated Results: Higher overall measures of pain, indicated by EvF, knee hyperalgesia, OFT and synovium analysis, are anticipated in intact female mice than in intact male mice. ORX mice will likely experience more allodynia/hyperalgesia than intact male mice and OVX mice will likely experience less allodynia/hyperalesia than intact female mice. Intact DMM female mice will have increased effusion-synovitis at a worse grade than intact DMM male mice. ORX males will experience less severe OA than intact male mice and OVX females will experience more severe OA than intact female mice.

Discussion: Anticipated differences between the pain response between male and female mice show that the use of exclusively male mice is a limitation in OA-associated pain research.

Conclusion: This novel study considers the role of sex hormones on the pain perception of OA.

Keywords: osteoarthritis; mice; hormones; estrogen; testosterone; pain; hyperalgesia; inflammation; ovariectomized; orchiectomized

Introduction

Osteoarthritis (OA) is a chronic and degenerative disease that affects the joints of the body [1]. Tissues of the joints are affected by cartilage degeneration, distortions in bone morphology and inflammation [2]. OA presents with clinical symptoms ranging from stiffness, tenderness, swelling, and inflexibility of the joints as well as localized or extensive pain [3]. This condition can result in a long-term disability and can require pharmacotherapy for pain management and inflammation, as well as the need for joint replacement surgery [4]. About 3.9 million Canadians who are 20 years and older live with OA, accounting for 13.6% of the population [5]. Additionally, OA is more prevalent in the female population (16.1% of those 20 years or older in 2016-2017) in contrast with the male population (11.1%) [2]. Risk factors that are considered systemic include advancing age, being female, as well as genetic or inherited traits [6]. Modifiable risk factors include obesity, comorbidity, occupational exposure, physical activity, and diet [6].

OA has both higher prevalence and severity in women, usually over the age of 50, than in men. It has been observed that women tend to have more joints affected and greater joint swelling [7]. Age is a significant risk factor for OA in women. This can be attributed to the fact that estrogen has been found to have a protective effect against OA [8]. Once women experience menopause, this protective effect is lost, and the onset of OA is more likely. Estrogen has the key

function of activating osteoblasts, which synthesize bone matrix and play a role in bone mineralization. Additionally, estrogen receptors have been identified within various joint tissues [9]. Specifically, estrogen receptors have been identified in cartilage cells (chondrocytes) which maintain the extracellular matrix [10]. They are also found in bone cells and play a role in bone turnover, which is relevant to OA progression [10]. This indicates that the binding of estrogen plays a role in the maintenance of these tissues, and a lack of estrogen could contribute to the severity of OA. In a systematic review, 11 out of 16 studies that investigated cartilage damage in ovariectomized (OVX) animals found significant damage compared to control animals [11]. The other studies either found no significant impact (4 studies) or a beneficial impact (1 study). Due to these hormonal differences between male and female mice, male mice tend to be more susceptible to developing OA after destabilization of the medial meniscus (DMM), a common method to induce OA in mice [8]. As a result, despite a higher prevalence of OA among women, male mice are primarily used for OA research, with only 20-30% of OA studies using female mice [12]. This standard may be a limitation in current OA research.

A primary area of concern regarding the use of exclusively male mice is in understanding OA-associated pain. Women also tend to experience higher levels of pain than men [13]. In fact, studies have shown that women experience more severe OA symptoms and progression of symptoms compared to male counterparts presenting with the same radiographic grade [7]. There is also evidence that a heightened pain response in female mice may play a role in preventing joint overuse and ultimately results in less severe cartilage damage [14]. Though the exact molecular mechanism that causes sex differences in pain is unclear, it has been proposed that differences in immune response and inflammation between males and females could contribute to the difference in pain perception. A comparison of the molecular composition of synovial fluid between males and females found that females have higher levels of inflammatory cytokines that could contribute to higher levels of inflammation and pain [15]. There is also evidence that pain pathways differ between males and females. For example, microglial activation seems to play a significant role in pain perception for males, but pain is established for females via adaptive immune cells in the spinal cord. These pathways are also sensitive to change depending on hormonal conditions, as females will use microglia instead when testosterone levels are increased [16]. Additionally, high levels of testosterone are associated with an increase in pain threshold [17]. Estrogen, on the other hand, has been found to increase pain intensity and perception [16]. The differing pain establishment pathways between sexes indicate that the use of exclusively male mice could hinder the broad-scale applicability of OA pain research to women.

Though several studies have investigated differences in OA pain perception between males and females, there is a lack of studies that look at this difference in the context of hormones [12,18,19]. As menopausal women have low levels of estrogen, understanding any differences in pain in the absence of sex hormones is a relevant concern. In this study, the limitations of using exclusively male mice in OA research will be explored. We hope to achieve this by providing insight into the differences in OA pain perception between male and female mouse models, and the role of sex hormones.

Methods

Animals

10-week-old female and male C57BL/6 mice will be purchased and will be either intact, orchiectomized (ORX) or ovariectomized (OVX). C57BL/6 mice have high genetic homogeneity, reducing variation between subjects [20]. OA can also be induced in this strain via DMM surgery [21]. They will be treated in accordance with the Canadian Council on Animal Care guidelines. Mice will be housed in groups, provided with nesting material, shelters and an environment that is large enough to meet their physical and behavioural needs. Standard operating procedures will also be developed to assess their health and treat common health problems that may arise [22].

Procedures

A total of 48 female mice will be used, split into four groups (n = 12): sham, sham + OVX, DMM, and DMM + OVX. A total of 48 male mice will be used, placed in the same groups as the female mice, but they will have undergone ORX instead of OVX.

Half of the female (n = 24) and male mice (n = 24) are purchased with OVX/ORX. Half of the OVX female (n = 12), ORX male (n = 12), normal female (n = 12) and normal male (n = 12) mice will receive DMM surgery on the right leg to induce post-traumatic OA. DMM is the standard method to study post-traumatic OA in mice. The DMM model shows many of the characteristics of OA seen in patients such as cartilage damage and ligament calcification. It also produces fewer cartilage and trauma defects compared to other methods such as anterior cruciate ligament transection (ACLT). In DMM surgery, the medial meniscotibial ligament (MMTL) is transected and this imitates the histopathology of OA, resulting in a highly consistent OA condition with a slower progression. Surgical DMM will be performed with an operating stereomicroscope to achieve more robust results and reduce unnecessary waste [23]. The remaining mice will receive a sham surgery. The sham group follows a similar surgical procedure as DMM, but it does not destabilize the medial meniscus which ensures no effects are caused by the surgery itself. All following measures will be performed by an experienced researcher who is blinded to the experiment groups.

Electronic von Frey

Following DMM and sham surgeries, all mice will undergo Electronic von Frey testing (EvF), a method used to evaluate mechanical allodynia. Measurements will be taken before surgery, and then 4, 8, and 12 weeks post-surgery. Mice will be placed in small cages individually with a mesh bottom. A single, unbending filament will be applied to the plantar surface of the hind paw. It will be applied with increasing force using a hand-held force sensor with a rigid metal until a paw withdrawal response is triggered. The apparatus will automatically record the force at which this reaction takes place, and this value will be termed the paw withdrawal threshold. Nocifensive behaviours such as licking, shaking of the paw and brisk paw withdrawal are deemed positive responses [24].

Knee Hyperalgesia

As a measure of pain, knee hyperalgesia measurements will be taken for all mice before surgery, and then 4, 8, and 12 weeks post-surgery. Mice will be restrained by hand, with the hind paw lightly held in place to ensure the knee is bent at the same angle for each mouse. One measurement will be taken for each mouse. A Pressure Application Measurement (PAM) device will be pressed against the medial side of the operated knee, while the assessor's thumb will be pressed lightly against the lateral side. Guided by PAM software, the assessor will apply constant force at 30 g/s up to a maximum of 450 g. The force at which the mouse withdraws its knee will be recorded. If this does not occur, 450 g will be recorded as the maximum force [25].

Open Field Testing

As a measurement of pain influencing locomotor and behavioural activity, open field testing (OFT) measurements of all mice will be taken before surgery, then 4, 8 and 12 weeks post-surgery [26]. OFT will be performed during daytime hours, at the same time each day, as described in Tatem 2014 [26]. The initial acclimation period will have each mouse placed in an individual testing chamber for 60 mins for 4 consecutive days on Week 0, with control data collection on Day 5 before DMM surgeries. The test conditions for timing will be for a total of 60 minutes on the day of data collection and the parameters collected are horizontal activity, vertical activity, movement time, total distance travelled, and rest time [26].

OARSI Scoring

All mice will be sacrificed at 12 weeks post-surgery and histological samples from the knee joint will be obtained to assess for damage. Joints will be decalcified in 10% ethylenediaminetetraacetic acid and then sectioned and stained with Safranin O/Fast Green. The samples will then be scored using the Osteoarthritis Research Society International (OARSI) scoring system [27]. Three sections from the center of the joint for each mouse knee will be scored and the average will be recorded to assess knee damage [27].

Analysis of the Synovium

The synovium, which lines synovial joints, becomes an area that is pathophysiologically affected due to inflammatory joint conditions known generally as synovitis [28]. A high prevalence of synovial inflammation has been seen with OA which is associated with pain and can even influence the onset of OA with structural progression [28]. Mice in all groups (n = 96) will be tested by collecting histological sections from the anterior portion of the joint in Week 12 which will be stained with hematoxylin and eosin, then mounted on slides [29]. A synovial scoring system with six parameters assessing synovial lining thickness, sub-synovial infiltration, vascularization, fibrin deposition, fibrosis, and perivascular edema will be used to assess each section [30]. Each parameter is assigned a score from 0 (normal) to 3 (severe) and totaled across all six to give a maximum score of 18 by two experienced researchers who are blinded [30].

Statistical Analysis

Statistical analysis for mechanical allodynia and knee hyperalgesia will use a linear mixed effects model, followed by a post-hoc pairwise comparison test. OFT, synovitis and OARSI scores will be analyzed using a two-way analysis of variance (ANOVA) between factors of sex hormones (intact female, intact male, ORX, OVX) and surgery type (DMM and sham). Then for all three independent data sets, a post-hoc Tukey's test will be performed.

Anticipated Results

OARSI scoring will likely show that DMM male and female mice will experience cartilage damage, but the sham group will not. This results in the DMM groups having significantly higher OARSI scores than the sham mice [29]. It is also predicted that DMM males will experience more severe OA than DMM females [12]. ORX males will experience less severe OA (less damaged joints) than intact male mice, resulting in lower OARSI scores than intact male mice [12]. OVX females will experience more severe OA than intact female mice, resulting in higher OARSI scores than intact female mice [12].

In the analysis of the synovium, synovitis will likely be present and will increase significantly in scoring for both male and female DMM mice compared to sham mice [30]. This results from DMM surgery and the progression of OA will result in inflammation. It is also predicted that intact females following DMM surgery will have increased effusion-synovitis at a worse grade and higher levels of pain than intact mice [31].

It is predicted that DMM male mice who are intact will likely experience more severe mechanical allodynia than ORX mice [17]. DMM female mice who are intact will

likely experience more mechanical allodynia than OVX mice [17]. At a similar severity of OA, intact male mice will likely experience less mechanical allodynia than intact female mice [17]. ORX mice will likely experience more mechanical allodynia than intact male mice and OVX mice will likely experience less mechanical allodynia than intact female mice [17]. The same results are anticipated for knee hyperalgesia measurements.

It is predicted that open-field testing will show trends for stationary behaviours and decreased locomotor activity between female and male mice due to pain perception [32]. This can present as a worsening change in gait over time and less walking time for the female DMM group compared to the OVX DMM and male DMM groups.

Discussion

The outlined anticipated results would further support the protective effects of estrogen against OA severity, and the detrimental effects of testosterone, as determined in previous studies [8]. Higher overall measures of pain, indicated by EvF, knee hyperalgesia, OFT and synovium analysis in intact female mice than in intact male mice is also predicted based on previous findings [12]. However, it is hypothesized that higher levels of pain in females prevent joint overuse and lower severity of OA as indicated by OARSI scoring. These results would suggest that there is a clear impact of sex hormones on pain perception in OA. There is evidence that estrogen increases pain perception and intensity, while testosterone reduces it [17]. This suggests that the use of exclusively male mouse models could be a limitation in OA studies. This could be especially important in studies regarding the management of OA-associated pain, as both pre- and post-menopausal women are not adequately represented.

Strengths

The proposed study considers the effects of sex-specific hormones on the pain perception of OA, which has been neglected in previous literature. The effects of OA and OA treatments are generalized when it is studied on male mice only.

Limitations

The physiological difference between mice models and the human body can lead to a discrepancy in results. Testosterone has been seen to have a protective effect against pain and the function of joints with OA in human males, but a detrimental effect in male mice [33]. Juvenile mice are used, which may be a limitation as OA is primarily observed in older ages. This study also has a limited sample size of 12 mice in each experimental group which can affect the robustness of results.

Conclusion

While male mice models are the current standard in OA research, there is evidence that physiological differences between female and male mice may pose a limitation. This study will provide further insight into these differences by exploring the role of sex hormones in pain perception. This research will improve our current understanding of OA-associated pain and increase the predictive value of animal models in OA research.

List of Abbreviations Used (If Any)

OA: osteoarthritis
DMM: destabilization of the medial meniscus
ORX: orchiectomized
OVX: ovariectomized
ACLT: anterior cruciate ligament transection
MMTL: medial meniscotibial ligament
EvF: Electronic von Frey
PAM: pressure application measurement
OFT: open field testing
OARSI: Osteoarthritis Research Society International

Conflicts of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This study did not require ethics approval as it has not been conducted.

Authors' Contributions

DP: contributed to study design and planning, drafted and revised the manuscript, and gave final approval of the version to be published.
AK: contributed to study design and planning, drafted and revised the manuscript, and gave final approval of the version to be published.
SC: contributed to study design and planning, drafted and revised the manuscript, and gave final approval of the version to be published.

Acknowledgements

The authors would like to acknowledge Ermina Hadzic, who provided insight and mentorship during the completion of this manuscript.

Funding

This study was not funded.

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Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Ermina Hadzic, Pierre Lemieux
Article Dates: Received Mar 31 24; Accepted May 21 24; Published Jun 20 24

Citation
Please cite this article as follows:
Parsania D, Khaton A, Chander S. The influence of sex hormones on osteoarthritis pain perception in mice. URNCST Journal. 2024 Jun 20: 8(6). https://urncst.com/index.php/urncst/article/view/603
DOI Link: https://doi.org/10.26685/urncst.603