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Review

Therapeutic exercise interventions in rat models of arthritis

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ABSTRACT

Arthritis is the leading cause of musculoskeletal pain and disability worldwide. Nearly 50% of individuals over the age of 65 have arthritis, which contributes to limited function, articular pain, physical inactivity, and diminished quality of life. Therapeutic exercise is often recommended in clinical settings for patients experiencing arthritic pain, however, there is little practical guidance regarding the use of therapeutic exercise to alleviate arthritic musculoskeletal pain.

Rodent models of arthritis allow researchers to control experimental variables, which cannot be done with human participants, providing an opportunity to test therapeutic approaches in preclinical models. This literature review provides a summary of published findings in therapeutic exercise interventions in rat models of arthritis as well as gaps in the existing literature. We reveal that preclinical research in this field has yet to adequately investigate the impact of experimental variables in therapeutic exercise including their modality, intensity, duration, and frequency on joint pathophysiology and pain outcomes.

Introduction

Arthritis is the leading cause of musculoskeletal pain and disability worldwide (Finn and Ferdousi, 2018), impacting an estimated one in five Canadians over 15 years of age (Badley et al., 2019). Though there are multiple available treatments for arthritic pain, there is insufficient clinical control of arthritis symptoms with existing pharmacological therapeutics (Yang et al., 2018). Movement-related pain is often reported by patients with arthritis, however, some forms of moderate exercise have been found to have protective effects on the joint in rodent models of arthritis (Pitcher et al., 2017). Exercise is often recommended to patients with arthritis by physicians and allied health professionals with limited guidance on the optimal frequency, duration, method, or intensity of movement required to alleviate joint pain and preserve joint integrity (Holden et al., 2021; Lopes et al., 2023; Sluka et al., 2018; Qaseem et al., 2017). Light to moderate therapeutic aerobic exercise has been found to improve pain in OA patients (O'Connor et al., 2015), however, clinical research in this field often relies on participant self-report of activity levels and lacks objective measures which could contribute to a more comprehensive understanding of the specific beneficial components of therapeutic exercise for arthritic pain. Due to the challenges associated with patient adherence to exercise regimens, preclinical studies provide an opportunity for researchers to investigate the impact of movement on arthritic pain outcomes in a carefully controlled environment.

Exercise has been shown to alleviate pain in the acute period after exercise via a phenomenon commonly known as "runner's high" (Polaski et al., 2019). Regular compression of the cartilage through movement is key to upholding the integrity of cartilage and prevention of damage (Sophia Fox et al., 2009) Preventative exercise has been demonstrated to prevent or delay pain onset in a murine Complete Freund's Adjuvant (CFA) model of rheumatoid arthritis (Lima et al., 2017). A reduction in mechanical hypersensitivity was also seen in rodent models of persistent pain (e.g. neuropathic, muscle pain models, etc.) with optimal pain reduction in studies which commenced voluntary movement paradigm between 6 and 8 weeks prior to injury (Grace et al., 2016; Leung et al., 2016; Sluka et al., 2013; Qaseem et al., 2017).

In preclinical studies which applied therapeutic interventions to other forms of chronic pain (Stagg et al., 2011; Wakaizumi et al., 2016) exercise has been shown to alleviate mechanical hyperalgesia. There is evidence suggesting that aerobic exercise plays a crucial role in the regeneration of damaged peripheral nerves and functional recovery

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after injury, which may contribute to this observed alleviation of corresponding pain outcomes following therapeutic exercise interventions. Following peroneal nerve damage, an exercise paradigm with twice daily low intensity movement at 5 m/min carried out over 10 weeks was found to lead to decreased levels of myelin-associated glycoprotein, a nerve growth inhibitor (Ghiani et al., 2007). Similarly, (Teodori et al., 2011) found that two weeks post-operation following sciatic nerve transection and repair, seven consecutive days of swimming exercise initiated generated significantly improved sciatic nerve regeneration compared to sedentary controls. It has been proposed that exercise-induced improvements to metabolic conditions within the local injury environment may prevent muscle atrophy and contribute to nerve regeneration (Aas et al., 2002). However, there is less information in the literature regarding therapeutic applications of exercise in chronic pain conditions like arthritis. Based on evidence in the literature which supports a potential role in which therapeutic movement may alleviate pain outcomes in arthritis, this review seeks to summarize existing findings in this field and identify gaps in the current literature.

Methods

A literature review of studies using rodent models of arthritis to investigate the impact of therapeutic movement on arthritis was conducted. A search was completed using Embase (Ovid), BIOSIS, Web of Science, and Scopus databases for English language publications. After title and abstract screening, an additional hand-search of reference lists of relevant studies was also performed. A total of 607 non-duplicate sources were retrieved from all databases in the search. Although the search strategy was open to all rodent models of arthritis, only rat models met criteria for inclusion in this review. After title and abstract and full-text screening, only 19 articles met final inclusion criteria without exclusion criteria (Fig. 1). A detailed search strategy was optimized for each database after the consultation of librarian Andrea Quaiattinni, MSc. The search strategies for each database can be found in the Supplemental Materials.

Inclusion criteria: The search required that the research was completed using a rodent model of arthritis (surgical, genetic, or chemical model), and included movement as a therapeutic intervention. Additional data on experimental conditions and outcome measures gathered by researchers were included in Supplementary Data. This review included sources that used regular forced or voluntary movement interventions of any kind. Exercise paradigms which included both a pre-training period and one-time exercise session were included in this review.

Exclusion criteria: Sources were excluded if they included the use of one-time movement interventions without pre-training, movement interventions that were preventative in nature (defined as greater than one week prior to the induction of arthritis model), or studies which used movement as a noxious experimental stimulus, rather than as a therapeutic intervention.

Intra-Articular models of arthritis

There is a significant diversity of arthritis models used by those investigating the impact of therapeutic movement paradigms on joint morphology or pain outcomes in arthritis (See Table 1). Among sources that met inclusion criteria for this review, CFA, Monoiodoacetate (MIA), and Collagenase models of arthritis were used. Between the chemical models of arthritis, there was great variability within doses used and total volumes administered. Doses in studies using MIA models ranged from 0.5 mg to 4.8 mg in saline, with total volumes ranging from 25 to 100 µl. Within sources which used CFA models, the dose administered also varied significantly. CFA models injected either 0.025 mg in 25 µl saline (single intra-articular injection in the knee) (Pitcher et al., 2017)

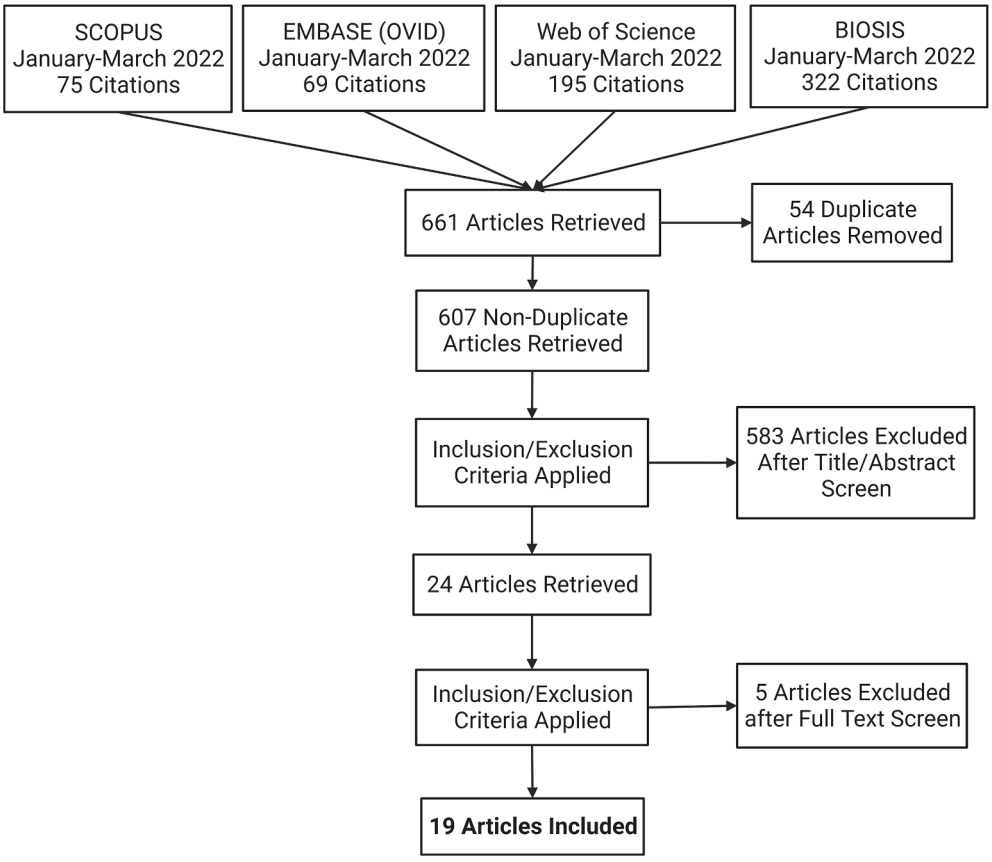

Fig. 1. PRISMA flow chart illustrating the sequence of database searches, screening steps, and final decisions on source inclusion.

Table 1
Frequently Used Rodent Models of Arthritis.

Model	Type of Arthritis	Species	Description	Benefits/Drawbacks	References
Monoiodoacetate (MIA)	Osteoarthritis (OA)	Rat or mouse	Chemically induced. Intraarticular MIA injection induces chondrocyte death. Leads to robust cartilage degradation and eventual bone remodeling, like in human OA. Easy to reproduce. Consistent hyperalgesia and allodynia between 4 and 5 weeks post-injection.	Useful and reliable model for the study of OA pain, but not mechanisms of cartilage degradation. Chondrocyte death is aggressive and not representative of the typical progression of OA in humans.	(Kuyinu et al., 2016; Lampropoulou-Adamidou et al., 2014)
Complete Freund's Adjuvant (CFA)	Inflammatory arthritis, Rheumatoid Arthritis (RA)	Rat or mouse	CFA is injected subcutaneously in the plantar surface of hindpaw or intraarticularly. Quick onset of pain behaviour, but joint damage only at later time points.	Clinically relevant pathophysiological changes, replicating those of RA (edema, cartilage erosion and bone deformation, pannus formation, etc.). Specific immune mechanisms still unclear.	(Holmdahl et al., 1986)
Medial Meniscal Tear (MMT)	Osteoarthritis (OA)	Rat or mouse	A surgical model of joint instability which produces mechanical hypersensitivity and allodynia ~ 4 weeks post-operation.	Useful model for evaluating therapeutic interventions. Rapid onset of pain symptoms, but requires surgical expertise. Possible issues replicability between test subjects and risk of infection.	(Kuyinu et al., 2016; McCoy, 2015)
Collagen Induced Arthritis (CIA)	Rheumatoid Arthritis (RA)	Rat or mouse	Induces rapid degradation of the cartilage matrix and produces inflammatory arthritis within ~ 3 weeks post-injection.	Rapid onset of pain-related RA symptoms can be beneficial depending on study design. However, rapid progression is not the typical progression of RA in clinical settings.	(Kuyinu et al., 2016; Lampropoulou-Adamidou et al., 2014)
Dunkin-Hartley Strain	Osteoarthritis (OA)	Guinea pig	Genetic model allowing for the natural induction of OA pathology at approximately 18 weeks of age due to a genetic predisposition to wear and tear in the joints.	Has the benefit of requiring no specialty intervention and having a natural progression of OA pathology. However, takes longer to develop and natural variability between animals in progression of pathology and symptoms.	(Bapat et al., 2018; Kuyinu et al., 2016; Lampropoulou-Adamidou et al., 2014)

or 1 mg in 100 μl saline (this study used two injections; one injection of 0.5 mg in 50 μl saline intradermally in the tail tip and then the second injection administered to the femorotibial or tibiotarsal joint 21 days later) (Gomes et al., 2014). Apart from the study by Gomes et al. (Gomes et al., 2014), all other sources in this review used intraarticular injection of a chemical agent to stimulate a model of arthritis in rats. The study conducted by Hong et al. (Hong et al., 2019) was the only publication identified by this review which adopted the collagenase model; however, authors did not report the amount or total volume of injected material.

Overwhelmingly, the MIA injection model of osteoarthritis (OA) was the most frequently used (79% of all sources in this review used an MIA model). The dose of MIA and CFA varied significantly between research groups. Multiple groups have provided evidence that the dose of either compound impacts joint pathology, disease progression, and resulting pain behaviour outcomes (Bourassa et al., 2020; Gomes et al., 2013). Few studies that met inclusion criteria used models of inflammatory arthritis so it was not possible to draw comparisons between OA and inflammatory arthritis models. In conclusion, there is a lack of consensus regarding the model and dose used to simulate various forms of arthritis in rodent models which induces a wide spectrum of outcomes, which limits researchers from performing *meta*-analysis or drawing definitive conclusions from this area of research.

Both Sprague-Dawley and Wistar strains of rat were adopted by studies which met inclusion criteria for this review. Authors found no apparent differences in reported outcomes after therapeutic exercise interventions during analysis. However, due to the number of variables in this this field of study, it is important that future investigators in this field consider the ways in which strain-dependent differences may also influence outcome measures. Preclinical research investigating the impact of exercise paradigms as a therapeutic intervention in rat models of arthritis have wide ranging experimental conditions which limit the transferability of findings between researchers and to clinical applications. This review provides an overview of factors which vary widely between research groups and may influence whether therapeutic movement paradigms are found to be beneficial to the reduction of pain and pathophysiological changes to the joint in rat models of arthritis. The lack of consensus on the optimal conditions of preclinical exercise paradigms prevents researchers from drawing conclusive, easily replicable findings, and inhibits the generation of novel evidence-based guidance on exercise regimens for patients suffering from arthritis.

Forced exercise paradigms

It is well established in the literature that exercise induces a wide range of immune-modulating activities through alterations to several immune related pathways (Leung et al., 2016; Sluka et al., 2018; Tian et al., 2021; Yang et al., 2018; Yang et al., 2018) which could in turn influence the degree of local inflammation at the impacted arthritic joint or alter central mechanisms for pain processing. For instance, in a rat MIA model of OA, therapeutic exercise has been found to induce changes to the NF-κB pathway (Yang et al., 2018) which is a key regulator of gene expression in multiple components of innate and adaptive immunity.

The modality of exercise as well as the environment in which animals are assessed can easily become a confound in the study as it will influence the stress level of the animal. The stress of the forced movement task may influence pathophysiological outcomes through the combination of immune (Fig. 2), biochemical, physical, and genetic factors (Kohn et al., 2016).Experimental factors including handling stress (Mogil, 2009), the sex of the experimenter (Sorge et al., 2014), and light conditions during experimentation (which alter cortisol levels) (Cifuentes et al., 2010) are all variables which may alter outcomes. As a result, these confounding variables, which are prevalent in this field, may interfere with the validity of findings in the literature.

Forced exercise was the preferred mode of therapeutic exercise intervention among sources gathered in this review, with 80% of included sources describing a forced movement paradigm (Allen et al., 2017; Boudenot et al., 2014; Chen et al., 2020; Cifuentes et al., 2010; Fallah Mohammadi et al., 2013; Gomes et al., 2014; Hong et al., 2019; Martins et al., 2019; Nam et al., 2017; Park et al., 2016; Saito et al., 2017; Tian et al., 2021; Walsh and Stocks, 2017; Yang et al., 2018; Zhang et al., 2018). Overwhelmingly, treadmill use was the preferred method of forced movement paradigm (93.75%). As opposed to voluntary movement, forced movement provides the benefit of controlling for movement velocity during exercise sessions. However, this approach comes with multiple disadvantages. Forced movement requires a form of

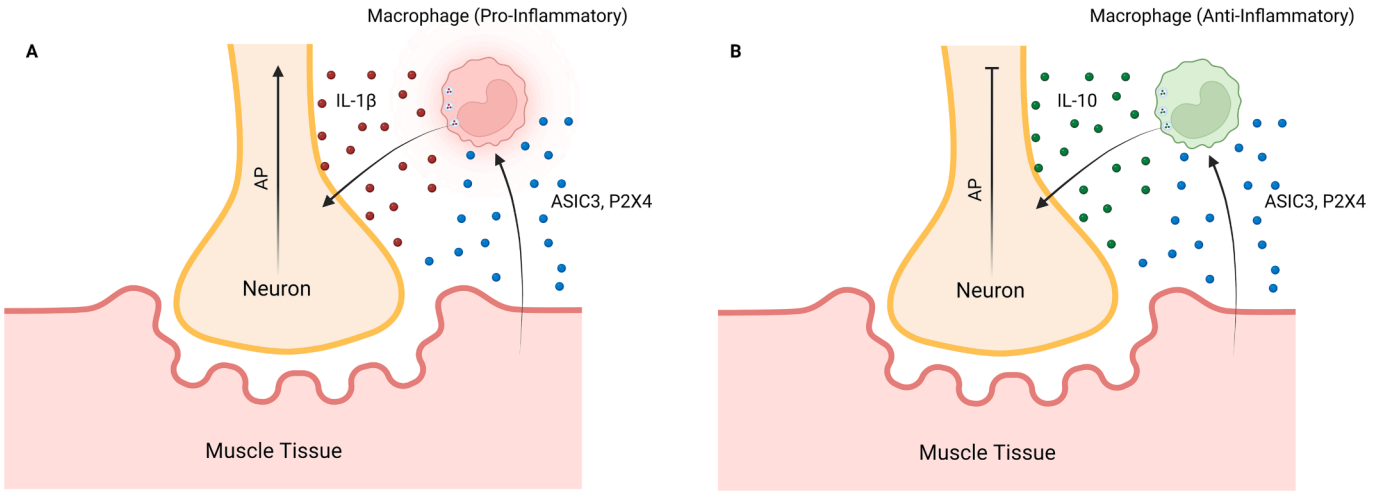

Fig. 2. Exercise-dependent immune modulation of peripheral processing of pain stimulus. (a) In sedentary animals, a pro-inflammatory macrophage phenotype is upregulated and releases more pro-inflammatory cytokines into the local injury environment. (b) Post-exercise, an anti-inflammatory macrophage phenotype is upregulated, releasing anti-inflammatory cytokines within the local injury environment (Sluka et al., 2018).

reinforcement to prompt the rodent to advance on the track, especially at the difficult-to-maintain moderate or high velocities used in most identified sources. Negative reinforcement traditionally requires the use of an electrical grid at the end of the treadmill, with a small electrical discharge on the tail of the rodent if they are not maintaining appropriate movement levels compatible with the set speed of the treadmill. Only 20% of studies using forced movement paradigms reported their use of a shock grid. Only one source (Hong et al., 2019) reported that no stimulus was required to promote movement behaviour. Alarmingly, 66.67% of sources did not report the method of reinforcement used to promote movement, which is an obstacle for potential future efforts to replicate findings. Forced exercise paradigms require an increased labour demand on experimenters and increase the potential for human-animal confounds in pain behaviour outcomes when compared to voluntary therapeutic exercise paradigms which limit such potential confounds including animal handling stress (Mogil, 2009).

Within studies that investigated the role of therapeutic exercise on pain behaviour or pathophysiological outcomes in arthritis, the mode, duration, frequency, and velocity of movement varied widely. The method of reinforcement used in forced movement paradigms is valuable information which may play a role in determining outcomes. It is well established in the literature that stress and fear can induce analgesia (Mogil, 2009; Terman et al., 1984). For replicability purposes, it is essential that the method of forced exercise is reported in detail. For instance, multiple authors (Fallah Mohammadi et al., 2013; Cifuentes et al., 2010; Nam et al., 2017; Park et al., 2016; Tian et al., 2021) reported the use of a treadmill for forced exercise paradigms but do not detail the reinforcement paradigms used to promote rodent movement.

Voluntary exercise paradigms

Voluntary wheel running allows the stress of forced movement to be avoided at the expense of no longer being able to control the velocity, duration, or frequency of movement. As a result of being unable to control for these variables, it is selected as a mode of therapeutic movement in experimental designs far less frequently than forced movement. Only 21% of sources identified in this review used voluntary movement paradigms to study the impact of therapeutic exercise on arthritis outcomes (Chen et al., 2020; Cormier et al., 2017; Pitcher et al., 2017; Townsend et al., 2022). Although some sources identified in the review explicitly stated their decision to use voluntary running paradigms was done to reduce the impact of stress-induced analgesia, only one source included measures of stress. Pitcher et al. (Pitcher et al., 2017) was the only source identified in the review to investigate the role of stress in a voluntary therapeutic exercise intervention using a rat model of OA by assessing serum levels of cortisol. Authors in this study stated that voluntary wheel running reduced stress when compared to sedentary controls. Cortisol is not only important to the psychological aspect of pain processing but also to joint pathophysiology in arthritis, with elevated cortisol from altered light/dark cycles increasing cartilage loss and damage in a collagenase model of OA (Hong et al., 2019). There is a growing base of evidence from preclinical studies of other chronic pain disorders which suggest that voluntary exercise reduces the impact of stress-based analgesia and/or hyperalgesia (Terman et al., 1984; Mogil, 2009).

Variables within movement paradigms

Within the exercise paradigm itself, frequency, duration, and intensity are key variables which vary greatly between research groups. Voluntary therapeutic exercise paradigms are unable to control for frequency or velocity of movement, and frequently do not report on average duration, frequency, or velocity which limits transferability and replicability of findings.

Frequency: Many preclinical studies investigating the role of exercise on arthritis outcomes incorporate a frequency of exercise that has limited clinical relevance. The frequency of therapeutic movement ranges from three days per week (Martins et al., 2019) to as often as three times per day (Walsh and Stocks, 2017). Investigating paradigms that include a frequency of exercise that is inaccessible to the average patient is counterproductive to potential application in clinical settings. No voluntary therapeutic movement paradigm included in this review reported frequency of use of the running wheel during times when it was accessible.

Duration: As is the case for frequency, it is important that the duration of therapeutic movement is well reported for the purpose of replicability. Duration is a key variable to consider when designing studies with the intent of translation to human populations. Duration in forced movement paradigms ranged from 20 to 90 min per session, but voluntary exercise paradigms allowed ad libitum access to wheels for anywhere from 2 to 12hrs. However, one study (Chen et al., 2020) did not report the duration of access to the running wheel.

Velocity: The velocity of movement varied widely between research groups cited in this review (which ranged from 11 to 28.6 m/min, with voluntary groups rarely reporting velocity data). Many sources identified in this review adopted forced running paradigms that included very

high velocities that are difficult for rodents to maintain over sustained periods. Further, some researchers found that they were only able to find significant differences at moderate or high intensities (Cifuentes et al., 2010; Townsend et al., 2022; Walsh and Stocks, 2017) whereas other researchers found no significant effect of movement velocity on outcome measures (Pitcher et al., 2017). Although voluntary exercise paradigms with running wheels often report usage statistics including average or maximum velocity and total run time, neither maximum velocity nor total run time was reported by any study in this review that used voluntary movement paradigms (Chen et al., 2020; Cormier et al., 2017; Pitcher et al., 2017; Sophia Fox et al., 2009; Townsend et al., 2022).

However, Townsend et al. (Townsend et al., 2022) reported that the naturally "high" velocity running groups (average of 16 m/min) showed the greatest alleviation of mechanical hypersensitivity when compared with the lower velocity running group. Though authors reported that a higher velocity of running was required to attenuate mechanical hypersensitivity, lower intensity running also diminished OA bone pathology via trabecular bone loss and bone remodeling which is typical of OA (Townsend et al., 2022). These findings are consistent with observations in the clinic that radiological markers of arthritic severity are not reliable indicators of the level of pain experienced (Cubukcu et al., 2012; Kohn et al., 2016). Townsend et al. (Townsend et al., 2022) found no significant difference in trabecular bone loss and bone remodeling between the two therapeutic exercise intensities, which may suggest that even low velocity therapeutic exercise could be effective at preventing bone loss and remodeling in OA, which are important factors in clinical assessment of whether total joint arthroplasty could be beneficial to patients with arthritis (Kohn et al., 2016). Further investigation is required to review the potential use of low velocity therapeutic exercise interventions for clinical populations who would like to avoid invasive surgical intervention like total joint arthroplasty.

There is evidence that the higher velocity required for the reduction of mechanical hypersensitivity in rat models of OA may be due to endogenous opioid related mechanisms in key areas of reward centres in the brain including the rostroventral medulla (RVM) and the periaqueductal grey (PAG) (Fig. 3). This finding is supported by observations of attenuated mechanical hypersensitivity or return to symmetrical distribution of hindpaw weight bearing in high-velocity therapeutic exercise groups (Townsend et al., 2022), and observations of resumption of pain related behaviours in high-velocity therapeutic exercise groups following systemic administration of opioid antagonist naloxone (Allen et al., 2017; Sluka et al., 2018; Stagg et al., 2011). Sources identified in this review provide evidence that high velocity exercise paradigms dampen neuronal inputs from the osteoarthritic knee joint through endogenous opioidergic pain inhibition, which supports growing evidence of a neuropathic component of OA (Bourassa et al., 2020; Dimitroulas et al., 2014; Grace et al., 2016; Power et al., 2018; Wakaizumi et al., 2016). This proposed opioidergic mechanism of pain inhibition in OA is consistent with findings from other rodent models of neuropathic pain (Stagg et al., 2011) as well as evidence from clinical populations (Power et al., 2018). The literature in this field suggests that velocity of therapeutic movement is a determining variable in pain and pathophysiological outcomes in rat models of arthritis, however, many potentially confounding variables and lack of replication in this field have left gaps in this literature.

Stress-induced analgesia

Stress-induced analgesia plays a role in pain processing in preclinical models of pain (Terman et al., 1984). It is well known that forced running paradigms can be highly stressful (Mogil, 2009), yet only 5% of sources found in this review incorporated assessments of stress. Furthermore, many conditioned forced running paradigms can activate reward pathways in the rodent brain which may interfere with pain processing at the level of the spinal cord (Castillo-Ruiz et al., 2010). The experimental designs adopted by most preclinical researchers in this field render it impossible to conclude whether pain reduction is a product of exercise-induced hypoalgesia, or if the forced running component of most preclinical studies investigating exercise is promoting stress-induced analgesia in animals.

Stress can increase or decrease pain perception and consequential behavioural outcomes associated with pain depending on contextual variables (Mogil, 2009; Terman et al., 1984) (Fig. 4). To use preclinical models to investigate the impact of exercise on outcomes in arthritis, future research must include easily replicable and clinically relevant movement paradigms, assessment of pain behaviour outcomes and investigation of the impact of stress-based analgesia on said pain outcomes.

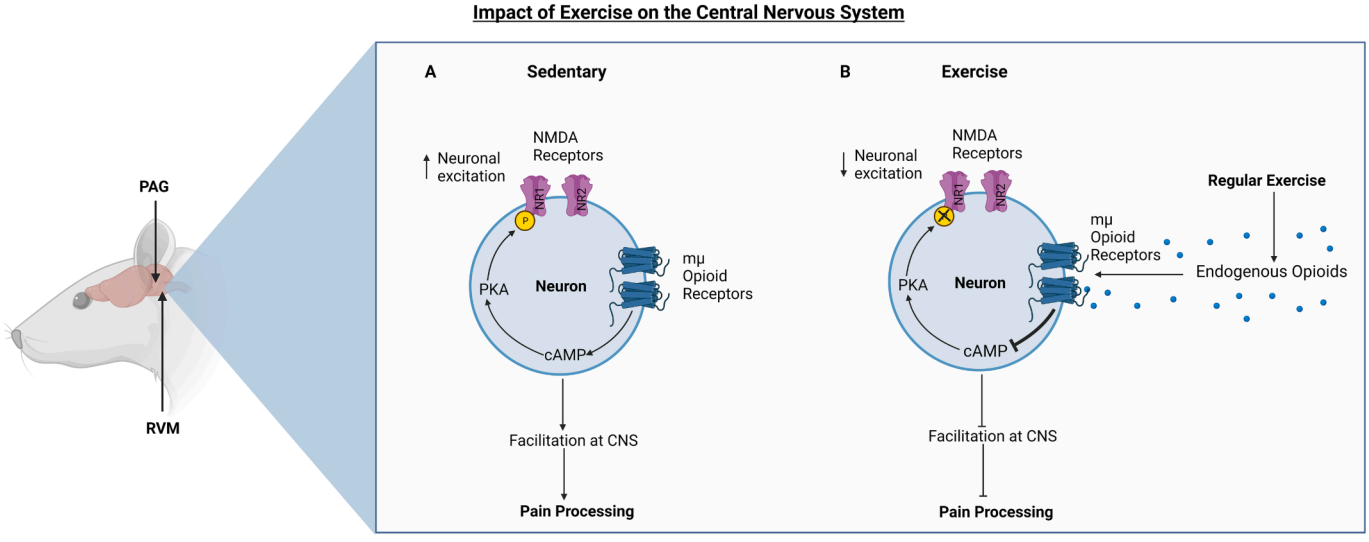

Fig. 3. Exercise induced endogenous opioid release inhibits phosphorylation of NR1 (NMDA receptor) in the rostroventral medulla (RVM) and periaqueductal grey (PAG), preventing facilitation and further pain processing in the central nervous system (CNS) (Sluka et al., 2018). (a) The molecular pathway in which inactivated neuronal μ-opioid receptors permit cAMP-Protein Kinase (PKA) pathway mediated NMDA phosphorylation, which consequently permits neuronal excitability, enhanced facilitation of pain processing in key brain areas including the RVM and PAG. (b) The molecular pathway in which endogenous opioids (μ-opioid receptor agonists) inhibit cAMP-PKA mediated NMDA phosphorylation in key pain and reward-associated brain areas, inhibiting neuronal hyperexcitability (key to central sensitization) and subsequent pain processing in the central nervous system.

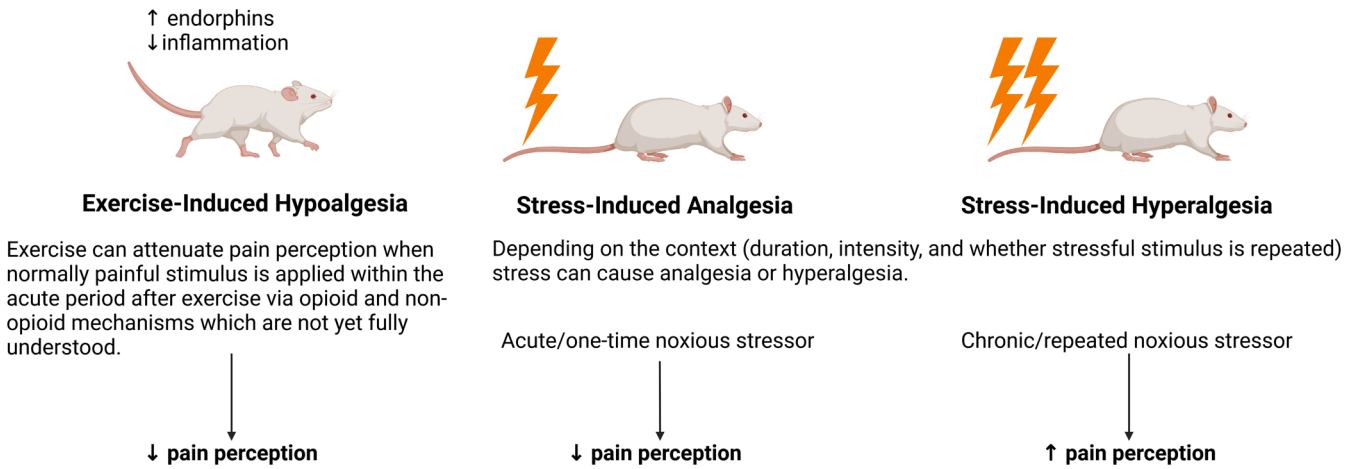

Fig. 4. Competing variables contribute to pain perception in the investigation of the impact of exercise interventions in rat models of arthritis. Exercise induced impacts on pain perception as well as stress-related experimental confounding variables in the study of exercise interventions for animal models of pain.

Outcome measures

In many cases, studies investigating the impact of exercise using rodent models of arthritis assess outcomes which are pain adjacent. For instance, many researchers investigate alterations to joint pathophysiology, which is known from clinical observations to not always correspond to pain outcomes (Cubukcu et al., 2012). Although there is an abundance of publications concerning joint degradation and molecular mechanisms by which therapeutic exercise may preserve joint integrity, it is not necessarily true that this translates to reduction in mechanical or heat hypersensitivity or cold allodynia.

Changes to peripheral tissues and joint pathology: Therapeutic exercise intervention has also demonstrated significant preservation of bone structure within the arthritic joint in preclinical models (Allen et al., 2017; Boudenot et al., 2014; Cormier et al., 2017) (Fig. 5). Additionally, therapeutic exercise has also been found to downregulate inflammatory JNK/NF-κB signaling, reducing intra-articular synovial fluid levels of TNFα, IL-1β, and IL-6 (Chen et al., 2020). In the MIA model of arthritis, 16 sources found that aerobic exercise alters the expression of molecular pathways, downregulating genes in the matrix metalloproteinase (MMP) family and upregulating anabolic ACAN, COL2a1, and TIMP3 in cartilage tissues. However, Saito et al. (Saito et al., 2017) found that their forced exercise paradigm expedited cartilage erosion when compared to their sedentary control group. No single component critical to the success of therapeutic exercise for this application has been identified by this review, apart from regular and consistent movement. To elucidate which variables may be critical to pain reduction or joint preservation, researchers will need to design more sophisticated

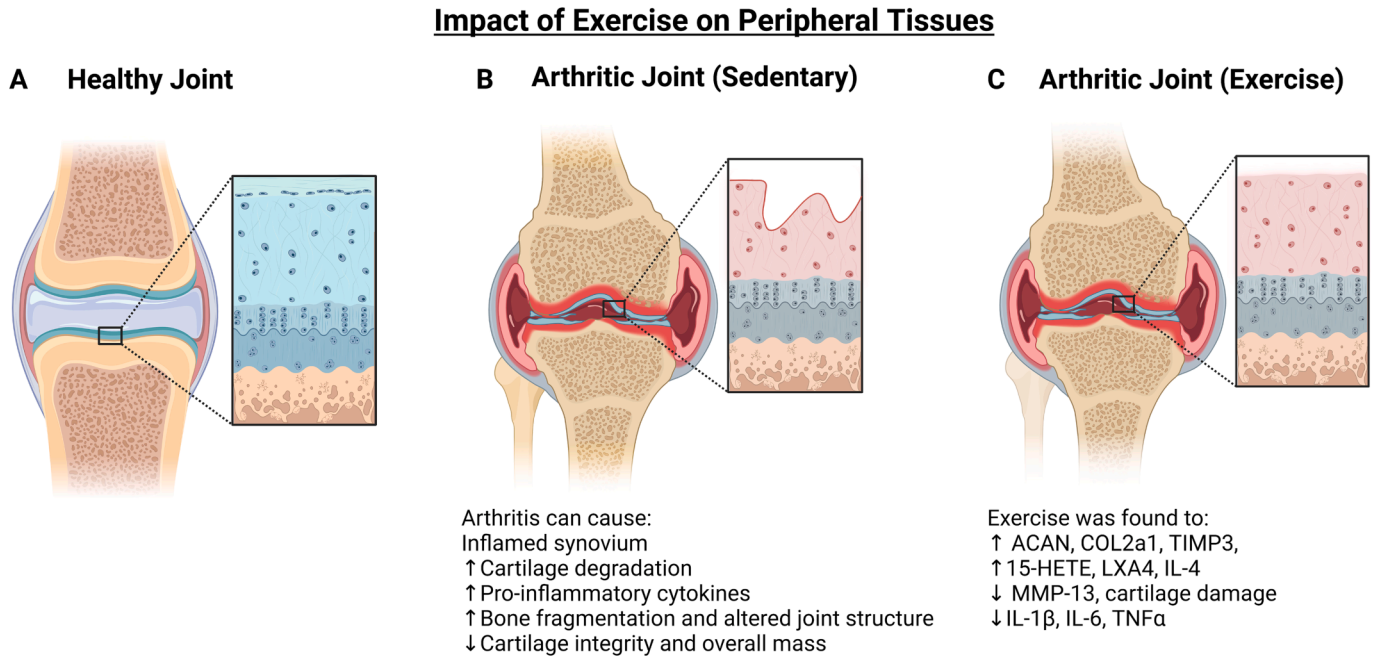

Fig. 5. Visual representations of therapeutic physical activity-modulated outcomes to joint tissues in rat models of arthritis. (a) A model healthy non-arthritic joint with intact cartilage and stable tissue homeostasis. (b) A model arthritic joint without aerobic exercise intervention with associated pathophysiology and inflammation. (c) A model arthritic joint with regular aerobic exercise intervention, exhibiting preservation of cartilage integrity and delayed progression of typical tissue degradation and inflammatory outcomes in rat models of arthritis through downregulation of anabolic and upregulation of catabolic mechanisms in chondrocytes (ACAN, aggrecan; COL2a1, Collagen Type II; TIMP3, tissue inhibitor of metalloproteinase 3; 15-HETE, 15-hydroxyicosatetraenoic acid; LXA4, Lipoxin A4; IL-4, Interleukin 4; MMP-13, matrix metalloproteinase 13; IL-1β, Interleukin 1 beta; IL-6, Interleukin 6; TNFα, tumor necrosis factor alpha).

experimental designs which further reduce the impact of potentially confounding variables.

Changes to the central nervous system: Preclinical studies suggest that exercise may have long term beneficial effects on the endogenous opioid signaling in the rostroventral medulla, an area of the brainstem key to pain perception (Allen et al., 2017) (Fig. 3). In an MIA model of arthritis in which rats were subjected to a forced exercise paradigm, Park et al. (Park et al., 2016) found upregulation of GAP-43 (a protein associated with the growth and regeneration of nerves) when compared to their sedentary counterparts. In a spared nerve injury model of neuropathic pain (Jaken et al., 2011), GAP-43 was found to colocalize with CGRP positive afferents, which suggests that it may be involved in the regeneration of nociceptive peptidergic afferents. Although exercise has been shown to improve mental health in patients with various chronic pain conditions, potential changes to the central nervous system through therapeutic exercise have not been thoroughly investigated in preclinical models of arthritis.

Changes to pain behaviour outcomes: Sources included in this review overwhelmingly focused on molecular changes to joint structures as a result of therapeutic exercise in rodent models of arthritis. However, based on the growing understanding that clinical indicators of joint pathophysiology in arthritis are not correlated with functional outcomes or pain behaviour (Kohn et al., 2016), the findings of these studies may be limited in their potential applications to clinical environments without concurrent assessment of pain behaviour outcomes. Only 26% of studies that met inclusion criteria assessed mechanical hypersensitivity with hindpaw weight bearing, Paw Elevation Test (PET) or Von Frey filaments. A resumption of baseline hindpaw weight bearing was found with one (Pitcher et al., 2017), two (Townsend et al., 2022), or four weeks (Allen et al., 2017) of therapeutic movement intervention with forced exercise paradigms, but interestingly, Townsend et al. (Townsend et al., 2022) did not see the same return to baseline hindpaw weight distribution in their voluntary movement intervention group at any time point. Gomes et al. (Gomes et al., 2014) found that forced exercise was associated with a return to baseline mechanical hypersensitivity measures using the Paw Elevation Test (PET). It is critical that researchers in this field include assessments of pain behaviour in their experiments based on the established understanding that changes to joint pathophysiology in arthritis are not correlated with functional restoration or reduction of pain in clinical settings (Kohn et al., 2016; Townsend et al., 2022).

Discussion

Outcomes measured vary widely and included biomarkers of molecular joint damage and pain behaviour. Future studies will need to consider the importance of assessing behavioural outcomes, such as mechanical hypersensitivity and cold allodynia in conjunction with molecular markers of joint degeneration and local neurological damage. The use of animal models allows researchers to investigate the role of therapeutic movement in pain outcomes and pathophysiological changes to joint structure within highly controlled environments, but clinical translation is ultimately limited by species differences including disparate joint loading mechanics in quadriplegic and bipedal species. Only Saito et al. (Saito et al., 2017) reported that therapeutic exercise was not helpful and perhaps even damaging to joint pathophysiology within the context of rodent models of arthritis. It is important to acknowledge that the bias in scientific literature to only publish positive results may present a false narrative.

Experimental design and experimenter influence: This is a field of study that has largely not been automated through the use voluntary movement paradigms which would alleviate the confounds of human-animal interactions on animal stress levels which are essential to pain processing. Thus, the choice to adopt forced movement paradigms in this field limits the validity of measures of pain behaviour.

Investigation of sex differences: Furthermore, even though nearly 60% of individuals with arthritis are women (Badley et al., 2019), only 10% of identified sources in this review investigated the role of therapeutic exercise in rat models of arthritis with female animals. Although none of the studies which met inclusion criteria for this review included both male and female rats, it has been previously documented that in rats (Konhilas et al., 2015) and several strains of mice (Guidotti et al., 2016) female animals have been found to naturally exhibit greater voluntary wheel running behaviour. This naturally occurring sexually dimorphic behaviour in rodent models is a crucial component for consideration in future study designs investigating therapeutic exercise interventions for arthritis using rodent models, particularly for those using voluntary movement paradigms. This may also be an obstacle to future investigators who seek to design therapeutic interventions which may be relevant to clinical translation, as a multitude of social and cultural variables contribute to lower voluntary activity levels in women when compared to men (Seabra et al., 2013). The potential role of sex differences has gone uninvestigated by the literature and must be considered by future researchers in this field when designing experiments.

Problems with outcome measures: The outcome measures adopted by researchers may further limit the translatability of findings to supporting evidence-based clinical guidelines. For instance, radiographic grading of joint pathophysiology (e.g. via Lawrence-Kellgren grading) can support a diagnosis of arthritis, however, the extent of cartilage degeneration and joint pathophysiology in arthritis are not directly correlated with pain outcomes (Kohn et al., 2016; Qaseem et al., 2017). Many studies investigating the role of exercise in rodent models of arthritis investigate molecular and pathophysiological joint changes as indicators of successful intervention but do not investigate pain behaviour. We found in this review that most preclinical therapeutic exercise intervention studies in arthritis did not investigate pain behaviour outcomes, but rather, pathophysiological changes to the joint which may not translate to pain reduction or improved function. Future researchers in this field should direct their attention to behavioural measures of pain as outcome measures for therapeutic exercise interventions for arthritis, particularly spontaneous measures including for example the grimace scale, weight bearing, and the use of gait analysis techniques which will provide a more comprehensive measure of pain-related outcomes.

Clinical translatability: Recently there has been emphasis from funding sources including the NIH HEAL initiative which emphasizes the importance of using animal models with promising translatability to the clinic. This has promoted increased attention towards surgical models including the medial meniscal tear model. Furthermore, although minimal or non-weight bearing exercise including swimming are often recommended therapeutic interventions for individuals with arthritis, this review did not find any preclinical studies in this field which investigated this exercise modality. Future investigators in this field should consider the design of therapeutic exercise interventions and rodent models with attention to the potential clinical translatability of findings generated.

Limitations

Much remains to be investigated in this field. This review did not compare outcomes between inflammatory and osteoarthritis models because an overwhelming majority of studies adopted the MIA injection model of osteoarthritis. Inconsistent methodology between research groups is an obstacle to understanding which variables are responsible for such widely varying outcomes. In future studies, investigators must endeavor to produce standards in this field of work which allow for replicability and reproducibility of findings between researchers. These factors have prevented further comparison between individual sources in this review as sources differ too much to perform *meta*-analysis.

Conclusion

There is a widespread inconsistency and a resulting lack of consensus

among fundamental researchers investigating the role of movement on morphological, molecular, and pain behaviour outcomes in rodent models of arthritis. The frequency, duration, and intensity of movement in therapeutic exercise interventions for experimental arthritis models in rodents vary widely between research groups. These variables are often poorly reported in the literature, and, thus, pose a challenge to replication efforts. This lack of consensus among basic science researchers in the investigation of the impact of movement on joint pathology in rodent models of arthritis renders the findings of past work limited in their translatability to clinical settings. Further, these variables may be key determinants in the success of experimental therapeutic interventions in rodent models of arthritis. Future researchers will need to acknowledge gaps in the existing literature to investigate the question of how therapeutic movement interventions may assist in the prevention of joint degeneration (or accelerate it), depending on the parameters of these experimental paradigms. Studies in this field will also need to address the very realistic possibility that, like many other chronic pain conditions, there are significant sex differences that have not been accounted for in past experimental designs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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