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Review

Translational animal models using veterinary patients – An example of canine osteoarthritis (OA)

Outi Vainio*

Faculty of Veterinary Medicine, POB 57, 00014 University of Helsinki, Finland

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ABSTRACT

Background and purpose: The use of laboratory animals in pain research has powerfully contributed to our detailed understanding of the physiological mechanisms of pain. Animal models also represent an essential tool to screen and select novel drug molecules with potentially analgesic properties. Despite of the inevitable input of laboratory animal trials, recent studies have shown that animal pain models have repeatedly failed to predict clinical analgesic efficacy and adverse side effects of potential drug molecules in human pain patients. This paper provides a review of the laboratory animal models of OA, which have been developed to test efficacy of novel analgesics. The paper also presents spontaneous OA in canine veterinary patients, and methods to observe chronic pain in nonverbal dogs.
Methods: PubMed data base was searched as a reference list to locate most relevant articles. A number of 118 articles including 4 reviews were located. Web pages of 4 establishments and 2 private organizations were also accessed.
Results: The clinical expression and pathogenesis of naturally occurring OA in dogs is considered an analogous disease that occurs in humans, including pain and lameness. OA may occur in any joint in dogs as well as in humans. Primary idiopathic OA in dogs is rare, but certain breeds may be predisposed to it. For the most part, canine OA is considered secondary to acquired or congenital musculoskeletal disorders. Concomitant factors, such as aging and obesity, likely accelerate progression. However, mechanical factors appear to predominate in the etiopathogenesis of canine spontaneous OA. Both subjective (validated questionnaire) and objective (gait analysis) tools are available to measure OA related pain in dogs. Information on the prevalence of canine OA is limited, but rough surveys suggest that 11 million dogs in the United States and 5 million in Europe could suffer from OA. Ethical considerations concerning the use of privately owned dogs can be resolved by a careful experimental design.
Conclusions: Canine spontaneous OA could serve as a translational animal model that would more closely mimick clinical OA related pain conditions in humans. Privately owned dogs would make a solution to fix the gap between animal pain models and clinical trials when testing potential analgesic drug molecules. Close interdisciplinary cooperation would guarantee that both scientific and ethical intentions would be achieved.
Implications: The predictability of translational pain research would improve by using privately owned dogs as chronic pain models when testing novel analgesics.

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* Tel.: +358 9 19157316; fax: +358 9 19157300.
E-mail address: outi.vainio@helsinki.fi

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1. Introduction

The use of laboratory animals in pain research has powerfully contributed to our detailed understanding of the physiological mechanisms of pain [1], including the initiation, maintenance and termination of a painful signal. In addition, animal models represent an essential tool to screen and select novel drug molecules with potentially analgesic properties.

2. Experiments used to test analgesics in laboratory animals

Testing the potency of novel analgesic drug molecules in laboratory animals has involved both acute and chronic painful stimuli. In a classical acute pain assay, a noxious stimulus is applied to an extreme body part where a simple withdrawal response can be detected and scored [2]. Both the latency to the response and the response threshold are recorded in these trials. Distinguishing between unconscious spinal withdrawal reflexes [2] and conscious motor responses that involve supraspinal affective components [3] is vital when recording responses or their latencies. In inflammatory pain experiments, the noxious stimulus is induced by an algogenic chemical, such as formalin [4], carrageenan [5] and Freund's adjuvant [5], which are usually administered either subcutaneously or intraperitoneally [2]. Mediator-induced pain develops slowly but endures longer. Instead of an avoidance response, the affected animal expresses painful sensations by engaging in specific pain-related behavior which is associated with both the location of the discomfort and the species in question. Neuropathic pain models are frequently provoked by surgical constriction of a peripheral nerve lesion. Pain behaviors in neuropathic assays vary, the ultimate being self-mutilation [6,7].

When it became evident that simple experimental models were not analogous enough to complex clinical pain syndromes, researchers introduced complete disease models, such as cancer pain [8], post-operative pain [9–11], and surgically induced OA pain [12,13].

3. Challenges of translational pain research in laboratory animals

Despite of the inevitable input of animal trials in pain research, recent studies have shown that animal pain models have repeatedly failed to predict clinical analgesic efficacy and adverse side effects of potential drug molecules in human pain patients [1,14]. Several comprehensive reviews have covered the less satisfactory face validity of animal pain models [15–20], referring to the fact that the resemblance of symptoms of the pain tests are irrelevant to the clinical condition. Developing animal models that more closely mimick clinical pain conditions has become important in translational pain research [14,16].

4. OA models in laboratory animals

The term OA does not describe a single elusive disease, but rather it refers to a number of related and overlapping disorders where joint affliction and disability are prominent symptoms. In 1995, a consensus workshop defined OA diseases as consequences of both mechanical and biologic events that destabilize the normal coupling of degradation and synthesis of articular cartilage chondrocytes, the extracellular matrix, and subchondral bone [21]. The etiology of OA is largely unknown, but is most likely multifactorial [22]. In patients, OA diseases result in a common joint pathology [12] characterized by degeneration of the articular cartilage [23]; other affected articular tissues may also include subchondral bone, synovial fluid, synovial membranes, and surrounding periarticular soft tissues [22,24]. Because arthritis or OA is the most frequent musculoskeletal disorder [25,26], a variety of either induced or naturally occurring animal models of OA [27] have been developed to test the therapeutic potency of drugs [28].

Induced models in mice [29], rats [12,13,30], guinea pigs [31], rabbits [28,32], cats [33], dogs [34–36], sheep [37], and goats [23] focus mainly on the knee joint. Impaired functioning of the knee joint has been induced by surgical intervention [12,33,34,37], by chemically injecting an irritant into the joint [12,38], by blunt trauma [32], or by mechanical load [29,31,39], thus leading to an adaptive response which modifies the articular cartilage structure and contributes to OA. Because the knee joint is the most common target joint affected by OA in humans [22] this may have favored the preference of knee joint models. In addition, the knee joint is of considerable size and is easy to access, thus rendering it suitable for a model. Other joints have occasionally been added. Simmons et al. [40] introduced an OA model for the equine metacarpophalangeal joint, and genetically modified mouse models of OA are also currently available [41,42].

All mammals can develop degenerative joint diseases [43]. Naturally occurring OA has been described in mice [44–46], broiler chickens [47], guinea pigs [48–50], Syrian hamsters [51], non-human primates [52,53], aging cats [54,55] and dogs [55,56]. Salo et al. [30] found that chemically induced selective joint denervation in 2-month-old rats initiated a normal-like developmental process resulting in OA in the knee joint. The authors proposed that the loss of neurons with age may have contributed to a spontaneous developmental process, and therefore classified their OA model as normally occurring.

On the basis of insufficient data about the pathogenesis of OA pain, developing experimental models has been difficult [57]. The relevance of most animal models of OA is for the most part based on histopathological similarities to human disease [28]. This approach ignores differences in the speed of the degenerative process between an induced model and a naturally occurring disease. Most surgically induced models of OA have rapid and strict cartilage degeneration after manipulation. Whether these models can explain the pain mechanism of slowly developing clinical OA remains uncertain [57]. A swift development period also implies that fewer opportunities for experimental therapeutic assays are available. Spontaneous models, such as those seen in certain laboratory species and in privately owned dogs and cats, should offer a better opportunity to study the slowly progressive process that is characteristic to human OA [28,58], including the track records of drug-induced modification of disease progression. When Mao [16] recalled animal models mimicking clinical pain conditions, the author pushed for dialogues between researchers and clinical practitioners. For unspecified reasons, veterinarians with their animal patients were excluded from the call for discourse.

5. Canine spontaneous OA

Both the clinical expression and pathogenesis of naturally occurring canine hip dysplasia and OA are considered analogous diseases

that occur in humans. Progressive and degenerative canine OA causes notable signs of pain, such as lameness and physical disability [56,59], rendering affected dogs reluctant to perform normal activities [60]. Pain and lameness may be acute or chronic [60,61], and OA may occur in any joint in dogs [55] as well as in humans [22].

Primary idiopathic OA in dogs is rare [61,62], but certain breeds may be predisposed to it [60]. For the most part, canine OA is considered secondary to acquired or congenital musculoskeletal disorders [62]. Concomitant factors, such as aging [63] and obesity [64], likely accelerate progression. However, mechanical factors appear to predominate in the etiopathogenesis of canine spontaneous OA [58,63].

A diagnosis of OA is based on clinical signs, physical examinations, radiographs, and synovial fluid analyses [61]. The approach to treating canine OA will vary based on its severity and location [55]. Management of OA involves a lifelong multimodal approach which aims primarily to alleviate pain and secondly to improve mobility [59], including activity control, weight management, physical therapy, nutritional support, and nutraceuticals [55,61]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the dominant medical intervention for canine OA-related symptoms [59], and the scientific literature provides strong supportive evidence for the use of certain NSAIDs [65]. In the United States, NSAIDs have the largest number of reported adverse effects in companion animals [66]. In Sweden, canine specific NSAIDs came on market in the late 1990s. Thereafter statistical survival rates of Swedish aging canines have increased [67].

Humans possess genetic risk factors that influence their risk or hip OA, and which may also affect their outcomes of OA [68], see also the review by Valdes and Spector [69]. In medium- and large-size dog breeds, recent evidence has shown that hip and elbow dysplasia-related OA is associated with polygenetically inherited developmental abnormalities [70–72]. In a current paper [73], four hip dysplasia-associated and two OA-associated single-nucleotide polymorphisms (SNPs) and nearby candidate genes were identified in dogs. The SNPs identified included those near known genes reportedly associated with, or expressed in, OA in humans [74,75]. In addition to pre-clinical drug testing, a canine model could provide an opportunity to identify more potential genes underlying natural OA in humans.

6. Translational canine model of spontaneous OA

In clinical trials, most measures of treatment efficacy involve patient-reported outcomes [76]. In non-verbal dogs, this is unattainable, so recognition of treatment response is a challenge. In veterinary medicine, the owner of the animal or a veterinarian or both detect and report the management response. Measures of OA-related outcome in dogs have been validated in blinded, randomized, and placebo-controled trials [77,78]. The Helsinki chronic pain index developed by Hielm-Björkman et al. [79] was certified using veterinarians and owners to assess signs of pain in dogs. The process resulted in the potential use of 11 multi-factorial behavior- and locomotion-related questions in the assessing chronic pain in dogs [80]. A further study [81] concluded that pain-naïve owners did not perceive signs of chronic pain in their dogs, but the authors suggested that the owners could learn the detection of signs of pain through training. That said, the dog owners could nevertheless detect pain diminish and return after starting and discontinuing NSAIDs, respectively. The canine brief pain inventory [77] used the subjective assessment of efficacy of treatments administered by a trained owner who completed a questionnaire both before and after the treatment period. The questionnaire was tested in a double-blind, randomized, placebo-controlled trial and was able to detect improvements in pain scores in dogs with OA treated with NSAID or placebo. A client-based clinical metrology instrument was initially validated for the evaluation of canine OA [78]. Validation was based on a prospective cohort study where the dog owners completed a questionnaire before a gait analysis on a force platform, which served as an external standard measure. The authors concluded that the instrument was worthy of continued investigation.

Gait analysis, measurement of ground reaction forces of each leg using a force plate, provides a quantitative description of quadrupedal gait [82]. Gait analysis provides a non-invasive assessment of lameness beyond subjective evaluation [83]. When necessary, an intra-articular anesthetic injection could serve to decouple gait mechanics from pain originating in other organs, such as the muscles or skeleton [84]. Several studies have established the use of force platform in gait analysis in healthy dogs of various breeds [83,85–89] or of a certain breed [90], including comparative gait analysis of two breeds [91,92]. The trotting gait was more sensitive than the walking gait for differentiation of dogs with low-grade hind limb lameness [93].

Gait analysis successfully served to detect acute pain in dogs; pain was provoked by synovitis which was induced by intra-articularly injected sodium urate crystals [94], or surgical intervention [82]. Effect of chronic pain on gait was distinguished in dogs with surgically induced hindlimb lameness [95]. Gait analysis was also used for detecting the effect of exercise in dogs with naturally occurring hindlimb OA [96], as well as for evaluating effect of surgical technique prior to and after reconstructive surgery on experimental dogs [97], and on veterinary orthopedic patients [98,99]. The method was also used to confirm the postoperative efficacy of NSAIDs in privately owned dogs which underwent a reconstructive cruciate surgery [100]. A three-dimensional kinematic canine hind limb model was recently created by adapting techniques and algorithms developed for humans [101].

Information on the prevalence of canine OA is limited [63], but a rough survey carried out in the Unites States suggested that approximately 20% of the canine population over 1 year of age suffer from OA [56]. Quessy [102] found that 30% of all dogs suffered from OA but the source of the information was not specified. In certain canine breeds, the prevalence of hip dysplasia ranged from 41% to 73% [103]. In 2007, the American Veterinary Medical Association announced on its home page [104] that there are 72 million dogs in the United States. If one-fifth of them are younger than 1 year, then 11 million dogs in the United States could suffer from OA. This number includes predisposition to OA in any joint. The Fédération Cynologique Internationale claims on its web page [105] that in 2009, approximately 35 million dogs lived in Europe. If the prevalence of OA in Europe is the same as that in the United States, then more than 5 million European dogs would be affected by OA.

7. Ethical considerations

The use of laboratory animals in biomedical research has been questioned. Sensitive societies have enlisted public opinion in support of legislation for the protection of animals in biomedical research. In 2010, the European Union adopted a new directive [106] to update the 1986 directive on the protection of animals used for scientific purposes. In the United States, the Health Research Extension Act of 1985 [107] provides guidelines for animal use. The aim to reduce the number of animals used in science is incorporated in both laws. The acceptance of privately owned animals as translational models would support this aim.

Pet dogs as scientific objects will *per se* foreground ethical inquiries. It is unacceptable to cause detriment or to risk the

welfare of privately owned animals. However, potential analgesics intended for human use could be tested on pet dogs in the same way as novel veterinary medicines. The European Medicines Agency has assigned rules governing medicinal products in the European Union, including veterinary products [108]; the United States Food and Drug Administration has similar regulations [109] for the development of veterinary products.

As there is a need to fill the gap between basic science and clinical implications [110–112], veterinary patients suffering from naturally occurring OA could provide the missing linkage. In an optimal case, the potential test medicine would be appropriate for human and animal consumption.

Scientific proof of the efficacy of an experimental medicine in canines may request inclusion of a placebo group. This demand could prove problematic but a careful experimental design could include a placebo group if a rescue analgesic could be offered in the event signs of unacceptable pain were observed in the dogs involved. There is no published information on the attitudes of animal owners toward medical trials performed on their pets, but such owners are aware that debilitating OA may lead to untimely euthanasia of their pet [113,114]. Anecdotally, decent and caring owners are known to be favorable to bringing their pets to clinical trials, which may promise the alleviation of pain for their four-legged family member.

Pain research carried out on animals mostly lacks discussion about the affective modality of pain. The description of pain by the International Association for the Study of Pain (IASP) Subcommittee on Taxonomy [115] relates to pain in humans. The IASP special interest group for the study of pain in animals is designated to pain in non-human species [116]. In veterinary medicine pain is not precisely defined. The American College of Veterinary Anesthesiologists has aligned itself with a declaration that an individual animal may or may not experience pain in response to nociception [117]; and further, that it is difficult to compare the experience of pain in animals to that in people. Molony and Kent [118] used the following working definition: animal pain is an aversive sensory and emotional experience representing an awareness by the animal of damage or threat to the integrity of its tissues.

The research community does not share exclusive scientific evidence of the affective modality of non-human pain. However, there is still less evidence of its absence, at least in mammals. In animals, affective dimension of pain sense most probably differs from that of humans. Although different, some kind of affective component of non-human pain would add a new element to the late-phase preclinical testing of medical candidates. Poole et al. [84] suggested that the emotional component of pain should be considered in pain assessment in preclinical laboratory animal models in the treatment studies of OA. The authors remind that the affective modality of OA pain in laboratory animals has no standardized clinical tests but they indicated that such a test should be developed using behavioral output. For pet dogs suffering from naturally occurring OA, validated methods of pain recognition do exist, including subjective (dog owner, veterinarian) [77–81] and objective (vertical force analysis) measures [82,83] but the methods do not discriminate the emotional component of pain. In clinical trials carried out on veterinary patients, both sensory-discriminative and affective-motivational modalities of pain could be distinguished in a careful experimental design where behavioral methods would be combined to neurophysiological tools, such as electroencephalographic recording [119]. Dogs have demonstrated special social and cognitive skills [120,121] that have developed through the domestication process. The close coevolution of dogs with humans has improved the interspecies communicative abilities of dogs [122–124], which would facilitate the objective detection of affective modality of pain in this special non-human species.

8. Conclusions

When improving the predictability of translational pain research, canine veterinary patients offer benefits over other models. Firstly, trials in animals with naturally slowly progressive and degenerative OA would increase the predictability of the model, and could therefore improve the predictive veracity for drug candidate selection. Secondly, in addition to their special coevolutionary character, dogs share both their living environment and way of life with humans, which make them the closest animal model to humans. Thirdly, there are more than 5 million OA-defected dogs in Europe and 11 million in the United States, thus ensuring that the number of pet dogs available is sufficient to perform controlled blinded randomized clinical trials within a reasonable time schedule. Fourthly, the inclusion of privately owned dogs in analgesic drug development programs would be a win–win situation for both parties.

It is difficult to find any serious objection to why we should not expand animal trials to include privately owned animals. Can we afford to refuse the use of pet dogs as a model in translational pain research?

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