Porcine models in pain research

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Introduction

Translational pain research in pigs only recently gained increasing attention (Fig. 1). This increase is expected to continue due to:

- **Limitations to translate results from rodents to humans [1,2]**
- **Similarity between pigs and humans, notably: the nervous system, the skin, metabolism, sequence homology, scaling. [3,4]**

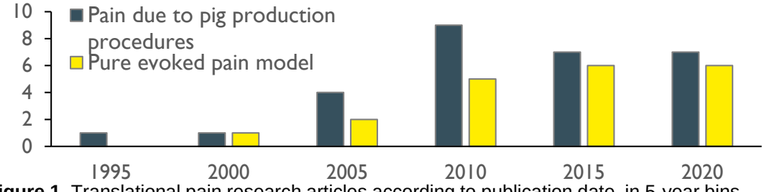

Figure 1. Translational pain research articles according to publication date, in 5-year bins.

Aim

To identify the translational pain models that are currently used in pigs and to compare these in terms of intensity and duration.

Methods

ProQuest, Scopus and Web of Science were searched systematically using the following search terms: “pain model” OR hyperalgesia, pig OR porcine OR swine OR piglet, NOT “guinea pig”. Included papers were divided into four categories, as shown in Fig. 2. The intensity and duration of the pain models was compared based on mechanical sensitization.

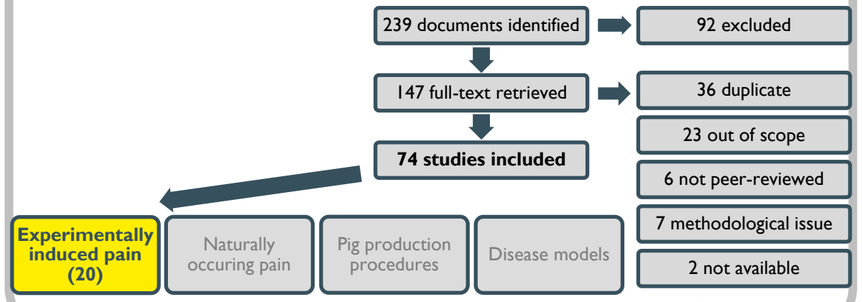

Figure 2. Flowchart of the identified, assessed, in- and excluded studies with categorization.

Results

Twenty studies used experimental pain to investigate the effect of pain or the effect of pharmaceutical treatment on experimental pain. These could be divided into surgical models, inflammatory models and neuropathic models. Intensity and duration of 10 models were compared based on mechanical sensitivity. Inflammatory models had the lowest intensity and these were typically reversible (Fig. 2b). The surgical models had a high intensity from model induction and measurements did not return to baseline by the end of the studies (Fig. 2a). The neuropathic models had a slow onset compared to the surgical models, but a similar intensity (Fig. 2c). Sensitization had not returned to baseline after 1 month.

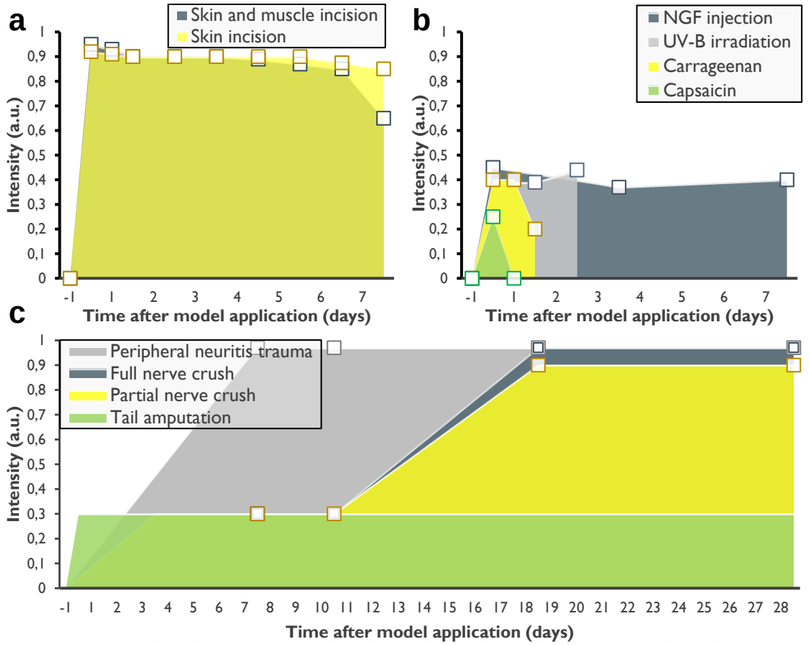

Figure 3. The duration and intensity of mechanical sensitization. The intensities were calculated using mechanical sensitization levels; 0 represents no mechanical sensitization and 1 represents a maximal increase in mechanical pressure sensitivity. A) Mechanical sensitization when pressure was applied to the wound was severe and prolonged in surgical models. B) Mechanical sensitization was comparable for most inflammatory models but insignificant for the capsaicin patch. C) Mechanical sensitization was severe for the nerve injury models, but delayed for nerve crush. Tail amputation led to mild sensitization. [5]

Results (cont.)

Table 1. All identified translational pain models and their manifestations.

Pain model	Manifestations
Full surgery	Lameness, vocalization, physiological and other behavioral indicators
Skin incision	Mechanical sensitization, increased (social) behavior score and vocalization
Skin and muscle incision and retraction	Mechanical sensitization, increased (social) behavior score and vocalization
Capsaicin	Thermal sensitization in small (27 kg) pigs, no significant mechanical sensitization
Carrageenan	Mechanical sensitization (up to 24 hours) and lesions (3 days)
UV-B irradiation	Mechanical and thermal sensitization (withdrawal and erythema)
Nerve growth factor (NGF) injection	Acute heat and prolonged chemical sensitization, prolonged decrease in mechanical activation threshold, increase in post-spike excitability and receptive field
Partial nerve crush	Mechanical sensitization from day 18, allodynia from day 7, behavioral indicators and motor deficit up to 10 days
Full nerve crush	Mechanical sensitization from day 18, allodynia from day 7, behavioral indicators and motor deficit up to 10 days
Peripheral neuritis trauma	Mechanical sensitization, allodynia, behavioral indicators, different open-field pattern
Surgical tail amputation	Mechanical sensitization, gene expression

Mechanical sensitization was the most reported outcome measure for the identified models. Other pain manifestations are summarized in table 1.
In order to push the field forward, we believe there is a need for increased focus on translatable pain indicators. Of particular interest are methods to investigate the peripheral and central nervous system.

Conclusions

- **Surgical pain models** cause severe sensitization, which is not comparable with human post-surgical pain. This is likely due to the test method.
- **Inflammatory models** cause mild and reversible sensitization, comparable to human inflammatory models, while allowing more invasive investigations.
- **Neuropathic pain models** in pigs are similar to those used in rodents. However, pharmaceutical testing yielded results similar to those obtained in humans, where rodent testing led to conflicting results.

Several porcine translational pain models have been developed and the potential of the pig in translational pain research lies in nervous system, metabolic, genetic, size and lifetime similarities [3, 4].

References

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