Suitability of Stimuli evoked Hypersensitivities in Hind paws as a Clinically Relevant Pain Behavioural Measure in Rat Model of Walker 256 Breast Cancer Cell-induced Bone Pain: An Overview

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Abstract

Metastases of breast cancer cells to the axial skeleton causes excruciating pain. The nature of pain hypersensitivities in metastasized bones is very complex due to the interplay of inflammatory, neuropathic and cancer-specific pain components. The existing drugs typically used to treat breast cancer-induced bone pain are inefficacious and often exhibit severe side effects. Hence, it remains to be an important goal of the ongoing research activities to seek novel analgesic compounds with better efficacy and tolerability. One of the key aspects in the process of understanding the mechanisms of pain progression and drug discovery to mitigate the hypersensitivities is employment of suitable preclinical animal models that mimic the complex human pathophysiology of breast cancer induced bone pain. Walker 256 breast cancer cell- induced bone pain model in rats is one such model that is known to show key resemblances to the clinical pain associated with bony metastases. The commonly used methods to assess pain hypersensitivities in Walker 256 cell- induced bone pain model in rats include stimuli evoked techniques like von Frey assessment and Randall-Selitto test. While other methods like assessment of gait parameters or spontaneous pain can also be used as beneficial complementary tools, this short review majorly sheds light on suitability of the stimuli evoked pain assessment methods in the hind paws of rats as being clinically relevant measures of assessing breast cancer induced bone pain in Walker 256 cell induced bony metastases.

Keywords: Walker 256; Breast cancer-induced bone pain

Introduction

Pain is a significant medical problem that co-exists with several diseases including various types of cancer [1]. Breast cancer cells metastasize from the tissue of origin and establish themselves in distant parts of the axial skeleton [2]. The cancer cells growing in the bone microenvironment cause osteolysis and sensitisation of the peripheral nerve endings innervating the bones, thereby causing excruciating pain [3]. Breast cancer-induced bone pain (BCIBP) causes severe morbidity because of the heterogeneous combination of inflammatory, neuropathic and cancer-specific components [4]. The existing analgesic/adjuvant medications are often insufficiently efficacious to combat this pain condition [5-

8]. Thus it is very important to develop and characterize suitable preclinical models of BCIBP so as to assist in drug discovery programs aimed at identifying novel compounds having potential to mitigate this often intractable pain condition. The rat model of Walker 256 breast cancer cell induced bone pain is a highly useful preclinical tool for assessment of mechanisms of BCIBP and for seeking novel analgesics in the treatments thereof, as it mimics key aspects of the human pathophysiology of this condition [8-11].

Discussion

Von Frey test using a series of filaments corresponding to different levels of forces, and paw pressure test also called as Randall-

Selitto testing using increasing force delivered via a blunt cone shaped pusher, are two of the most common behavioural tests employed in assessment of Walker 256 cell induced BCIBP in rats [9]. The plantar hind paw of rats, the anatomical region where von Frey and Randall-Selitto stimuli are applied, is mainly innervated by the tibial nerve and hence tibial bone pain sensations manifest as hypersensitivities in the plantar aspect of the hind paws [12-15]. Hence, the traditional and most commonly used method to measure tibial bone pain is assessment in the paws, with hundreds of studies prevailing in the literature using this protocol. By using intra-tibial injections of complete Freund's adjuvant in the tibiae of female Wistar rats, a study has elegantly established that the bone pain induced by activation of tibial nerves directly manifests as hind paw skin hypersensitivity [15]. Cutaneous tests like the von Frey testing and Randall-Selitto testing detect the current levels of pain and have high clinical relevance as used in humans [16-21].

A study involving the Department of Medicine of the University of Florida (Gainesville, USA) has validated that mechanically evoked pain is a highly relevant measure of the clinical pain intensity in patients with deep pain of muco-skeletal origin [22]. Similarly, a study conducted in Edinburgh Cancer Centre (Edinburgh, UK) also validated that assessing mechanical allodynia using von Frey filaments is a direct measure of cancer induced bone pain in humans [23]. Hence assessment of the stimuli evoked hypersensitivities in the hind paws is physiologically relevant assessment of bone pain. As per the previous studies published in journals like PAIN [24-26], The Journal of Pain [27,28], European Journal of Pain [29-31], Pain Medicine [32], Molecular Pain [33,34], Nature Neuroscience [35] and others, it is a traditional practice within the pain research fraternity to test the pain hypersensitivities in the paw, following inoculation of cancer cells in the tibia, without deploying other measures like gait or weight bearing parameters. Along these lines, a recent report suggested that a vast majority of around ~90% of the cancer induced bone pain studies in the literature using MRMT-1 cells in rats used the response evoked by the cutaneous stimuli applied to the foot as a measure of bone pain [36]. From the vast literature available on Walker 256 cell induced bone pain model in rats, inoculation of Walker 256 cell in the tibia always manifests as hypersensitivities in the hind paws, without any discordance in paw-tibia correlation being reported [8]. The majority of studies in the literature that used the Walker 256 breast cancer cell-induced bone pain model in rats, used the hind paw as a location to test hypersensitivity to evoked pain such as that induced by the von Frey test, rather than spontaneous or movement evoked pain [18-45]. There are many different studies very recently published, that used Walker 256 cells to induce bone pain in rats that only used stimuli evoked behavioural measures such as von Frey paw withdrawal thresholds in the hind paws, but not spontaneous movement evoked or weight bearing measures to assess pain hypersensitivities [35-60]. The vast experience of different laboratories conducting pre-clinical cancer-pain research around the world with the Walker 256 cell induced BCIBP model in rats strongly emphasizes on the suitability of stimuli evoked hypersensitivities in paws as the correct measure of bone pain in this particular model.

However, it is noteworthy that dissociation is observed in between skeletal pain behaviors and skin hypersensitivity in a male C3H mouse model of intra-femoral injection of NCTC 2472 osteosarcoma cells [61]. It is known that different types of cell lines or tumors exhibit distinct pain behavioral patterns [62]. It is the unique interaction between each of the cancers colonising the bone and the nerve innervation that predominantly decides the nature of pain manifestation [63]. On these grounds, a previous study highlighted the fact that neither spontaneous pain nor ambulatory pain is the best measure of cancer induced bone pain for all models triggered by different cancer cell lines in general [62]. It showed that intra-osseous injection of B16-F10 melanoma cell line in the femur did not produce either the spontaneous pain or the ambulatory pain. The bone pain induced by B16-F10 cell line manifested only as hind paw skin hypersensitivity. Similarly, C26 colon cancer cell line did not produce spontaneous pain behavior. Hence, the spontaneous or ambulatory pain are not the universal measures of bone pain at least in some models like B16 cell model and C26 cell model. In alignment to this pre-clinical animal based study, a clinical study of cancer induced bone pain also reported that in patients with breakthrough pain, which is commonly triggered by a stimulus [64], patients were not more likely to experience pain at the weight-bearing bone sites, compared to patients without pain [65]. Additionally, allodynia and gait behaviours are two independent phenomena. Neuropathic pain is one of the key components of cancer induced bone pain [4], and allodynia (measured by tests like von Frey) is a more reliable measure of the neuropathic pain component, rather than gait behaviours (weight bearing or spontaneous pain during ambulation) [66]. The changes in gait parameters can typically be due to the tendency of animals to avoid allodynia produced by contact of the paw with the floor [67]. The gait changes might not necessarily relate well to pain hypersensitivities [66-72]. There are several evidences that suggest that changes in gait parameters like guarding the hind paw during ambulation or changes in weight bearing are significantly driven by the adaptive changes and psychological influences (pain-avoidance and fear due to cognition), rather than the current levels of pain intensity [66-82]. Whereas, both the von Frey and Randall-Selitto tests that are also used in humans to assess pain hypersensitivities, detect the current levels of pain and have high clinical relevance [16-21]. This is probably one of the most important reasons why large number of published studies used stimuli-evoked methods like the von Frey and Randall-Selitto tests to assess pain hypersensitivities in the hind paws of animals following unilateral tibial inoculation of cancer cells.

Conclusion

The vast literature on Walker 256 cell induced BCIBP model in rats strongly suggests that stimuli evoked pain behaviours in the hind paws of rats is an appropriate measure of cancer induced bone pain in this particular model. However, a complementary assessment of measures like ambulatory pain, spontaneous pain or pain evoked by weight bearing on the hind paws of rats might add more value to the studies in future as these tests might be considered relatable to pain assessments in humans.

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