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Editorial comment

Multi-target treatment of bone cancer pain using synergistic combinations of pharmacological compounds in experimental animals

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In this issue of the Scandinavian Journal of Pain, González-Rodríguez and coworkers report about treatment of bone cancer pain using synergistic combinations of a dual enkephalinase inhibitor with various other drugs in experimental animals [1]. In the clinic, cancer, particularly that originating in the lung, breast and prostate, frequently metastasizes to bone, where it may cause pain, although not in all subjects or at all metastasized sites [2]. Bone cancer-induced pain may progress quickly from intermittent to continuous and further to breakthrough pain with episodes of extreme pain that occur spontaneously or that are induced e.g. by weight-bearing on the tumour-affected bones [3]. Additionally, bone cancer pain can be accompanied by mechanical hypersensitivity, due to which even gentle movements or touching the skin close to the tumour may induce strong pain [4,5]. These bone cancer-induced symptoms can severely reduce quality of life.

1. Experimental animal models in the study of mechanisms of bone cancer pain

Development of experimental animal models for the study of bone cancer pain has significantly advanced our understanding of underlying mechanisms. Behaviorally, animal models of bone cancer pain induce in the affected limb guarding and mechanical hypersensitivity mirroring continuous pain and tactile allodynia in the clinic [4]. In the bone of healthy control animals, sensory and sympathetic fibre innervation is most dense in the periosteum but also mineralized bone and marrow are innervated. Bone cancer induces sprouting of bone-innervating nerve fibres and the formation of neuroma-like features in periosteum [5]. Other peripheral changes that are likely to exert a role in bone cancer pain are upregulations of growth factors, cytokines and chemokines that are accompanied by pH changes and oxidative stress, all of which may influence excitability of sensory nerve fibre endings in the bone [3,5].

Among neurochemical and functional changes in the spinal cord dorsal horn of animals with bone cancer pain are an increased expression of a prohyperalgesic peptide dynorphin, increased neuronal activity, increased activation of astrocytes, and intense internalization of substance P (SP) receptors following innocuous mechanical stimulation of the affected limb [4]. Interestingly, inflammatory pain condition, such as that induced by complete Freund's adjuvant, leads to spinal up-regulation of SP and calcitonin gene-related peptide (CGRP), two neuropeptides found in nociceptive neurons. Neuropathic pain condition, such as that induced by peripheral nerve injury, leads to spinal down-regulation of these two neuropeptides. In contrast, bone cancer pain has a distinct spinal mechanism that differs from those of inflammatory and neuropathic pain as indicated by the finding that bone cancer pain failed to influence SP or CGRP levels in the spinal cord [3].

2. Treatment of bone cancer pain

Therapy of bone cancer pain, particularly when it is induced by bone metastases, involves multiple complementary approaches that include eradication of tumour using chemotherapy and radiation therapy, surgical stabilization of painful bones, decreasing potentially pain-promoting loss of bone e.g. with bisphosphonates, and administration of various analgesic compounds such as non-steroidal anti-inflammatory drugs and opioids [1–3].

3. Maximizing analgesic effect and minimizing side-effects with drug combinations

Unless eradication of cancer is successful, bone cancer and thereby bone cancer pain usually progresses and analgesic drugs need to be given for prolonged periods at increasing doses, due to which adverse effects of drugs provide a problem in the therapy of bone cancer pain. One approach to reduce side-effects and in parallel enhance pain-suppressive effects of analgesic compounds is to use combinations of drugs that reduce pain by acting on different targets and that have different, in the ideal case opposite, side-effects.

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4. Enkephalinase inhibitors in treatment of bone cancer pain

Met- and Leu-enkephalin are endogenous compounds released tonically at an injured site and suppressing pain behaviour due to action on mu and delta opioid receptors [1]. Met- and Leu-enkephalin are quickly degraded by two endogenous enkephalinases and therefore, their analgesic action is only of brief duration. However, administration of a dual enkephalinase inhibitor reduces degradation of Met- and Leu-enkephalin and thereby enhances and prolongs their analgesic effects particularly at the injured area, where they are tonically released [1]. In their present experimental animal study on bone cancer pain, González-Rodríguez et al. report that a combination of the dual enkephalinase inhibitor PL265 with various other analgesic compounds acting on different targets produces synergistic analgesic effects. This allows using lower doses of each analgesic drug and thereby drug-induced side-effects are reduced [1].

Conflicts of interest

The author declares no conflicts of interest.

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