Molecular Pain Imaging by Nuclear Medicine: Where Does It Stand and Where Is It Going?

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Pain is one of the most common reasons that patients seek medical attention. At least 20–25 % of the world population and 116 million people in the US report suffering from acute and chronic pain every year; indeed, the national annual economic cost associated with chronic pain is estimated to be \$560–635 billion (or \$2,000 for each American citizen); this figure includes medical treatment (\$260–300 billion) and lost productivity (\$297–300 billion) [1].

Unfortunately, the diagnosis and characterization of pain are a clinical challenge. A clinician's assessment of pain relies heavily on self-reporting by the patient; this, by its very nature, can be highly subjective. Conventional clinical imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) can only identify anatomical abnormalities; thus, they offer only low sensitivity and specificity for detecting pain-generating pathologies. Up to 80 % of asymptomatic patients have abnormalities on MRI, and the prevalence of anatomical abnormalities in asymptomatic and symptomatic patients is very similar. For example, abnormal processes in the cervical and lumbar spine, such as changes in the disk signal, disk displacement, nerve root compression, and facet arthropathy, are also observed in 64–89 % of asymptomatic patients. Because the final therapeutic decision is influenced by imaging results, this lack of specificity directly or indirectly contributes to delayed, ineffective, or even unnecessary treatment.

The need for a molecular imaging biomarker that is specific for pain-generating pathophysiology cannot be overstressed.

Molecular imaging aims to identify abnormal biological processes of cells or molecules, even in apparently normal anatomical structures. However, due to the complex biochemical pathways that underpin the mechanism(s) of pain, identifying a common molecular pathway responsible for chronic pain is a daunting task. Moreover, technical limitations mean that molecular imaging modalities have difficulty in identifying small structures, such as dorsal root ganglia and peripheral nerves, that may be responsible for neuropathic pain.

The aim of using molecular imaging technology to examine nociception is to detect abnormal physiologic activity at any point along the nociceptive pathway: this could be in the peripheral nervous system and/or the central nervous system. The molecular entities explored by imaging of painful neuropathic nerves may include (1) responsive cells, (2) inflammatory mediators and receptors, (3) ion channel expression, and (4) metabolic activity [2].

Molecular imaging can be used to interrogate the response of cell types in the vicinity of the nerve injury, as well as those in the CNS: for example, glial cells/macrophages involved in modulating chronic pain and Schwann cells that respond to nerve damage by cleaning up dead tissue and laying the groundwork for axonal regeneration. Attaching radioligands to translocator proteins (TSPO) makes it possible to identify the location of activated microglia and macrophages. Such radioligands include ¹¹C-PK11195, ¹⁸F-DPA-714, ¹¹C-PBR28, and ¹¹C-DAA1106. Activated Schwann cells and macrophages can also be imaged using radiotracers targeting the sigma-1 receptor, which is overexpressed by inflamed nerves.

Attempting to locate exacerbated inflammatory responses by radiolabeling a myriad of mediators produced by inflammatory cells, nerve cells, and Schwann cells is another way of identifying neuropathic nerves. Several neuropeptide analogs related to inflammation and pain have been radiolabeled. Examples

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include analogs or antagonists (SPA-RQ) of substance P. Other ligand receptor systems, such as calcitonin gene-related peptide, serotonin, bradykinin, brain-derived neurotrophic factor, vanilloid receptor VR1, *N-methyl-D*-aspartate, tyrosine kinase B, neurotensin, and cholecystokinin, are alternative candidates. Radiolabeled Cox-2 inhibitors are considered potentially useful; however, confirmation is needed because their location in inflammation models remains unclear.

Neuropathy and pain are caused by increased calcium and sodium flux across the nerve cell membrane, resulting in an altered excitation threshold, an abnormal action potential, and continuous firing. Saxitoxin, a paralytic shellfish toxin, was recently modified and radiolabeled with ^{18}F ; this toxin binds to voltage-gated sodium channels with nanomolar affinity. Thus, voltage-gated calcium channels in injured nerves can be imaged using a manganese MRI contrast agent.

Metabolic activity, as measured by ^{18}F -FDG avidity, in peripheral nerves has been observed in the lumbar spinal cord and sciatic nerves of patients suffering from pain. Continuously firing neurons and associated inflamed tissues are glucose avid. ^{18}F -FDG PET/MRI was also used to visualize neuronal metabolism in experimental animal models.

Although research into the imaging of chronic neuropathic pain is promising, actual implementation remains a challenge. For example, methods directed at ion channels can be potentially toxic. Other challenges include identifying the optimal components of human pain pathways, developing preclinical pain models that accurately mimic the human pain experience, and imaging small structures responsible for pain generation and propagation [1]. Hypersensitive nuclear medicine techniques that combine the sensitivity and specificity of molecular markers would be of great help. Therefore, the advent of a PET tracer for pain would open up potential new avenues for

imaging and may allow us to pinpoint distinct types of soft tissue abnormalities using PET/MRI.

Identifying pain generators will lead to a more intelligent approach to pain in that therapy can be guided. Should the successful imaging and identification of pain-causing structures/pathways become a reality, it would have a tremendous impact on the field of medicine and benefit millions of chronic pain sufferers. Despite its prematurity and infancy, image-based pain research needs to be dealt with in *Nuclear Medicine and Molecular Imaging* if it is to fulfill its potential in the fields of nuclear medicine and molecular imaging.

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Compliance with Ethical Standards

Conflict of interest Jung-Joon Min has no conflict of interest to declare.

Ethical statement The manuscript has not been published before or is not under consideration for publication anywhere else and has been approved by the author.

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