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Visualization of painful inflammation in patients with pain after traumatic ankle sprain using [^{11}C]-D-deprenyl PET/CT

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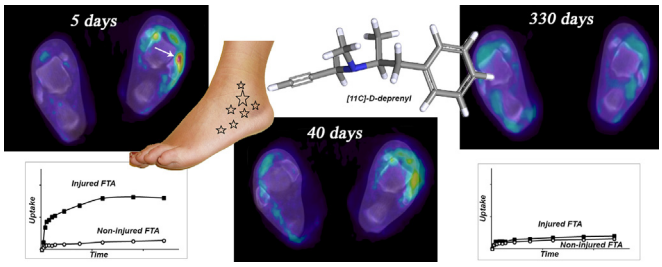
HIGHLIGHTS

- An increased [^{11}C]-D-deprenyl uptake is shown in painful locations after ankle sprain.
- Patients experiencing persistent pain had prolonged peripheral D-deprenyl uptake.
- The described method can visualize, quantify and follow pain generating processes.
- Such an objective correlate may represent a progress in pain research and management.

GRAPHICAL ABSTRACT



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ABSTRACT

Background and aims: Positron emission tomography (PET) with the radioligand [^{11}C]-D-deprenyl has shown increased signal at location of pain in patients with rheumatoid arthritis and chronic whiplash injury. The binding site of [^{11}C]-D-deprenyl in peripheral tissues is suggested to be mitochondrial monoamine oxidase in cells engaged in post-traumatic inflammation and tissue repair processes. The association between [^{11}C]-D-deprenyl uptake and the transition from acute to chronic pain remain unknown. Further imaging studies of musculoskeletal pain at the molecular level would benefit from establishing a clinical model in a common and well-defined injury in otherwise healthy and drug-naïve subjects. The aim of this study was to investigate if [^{11}C]-D-deprenyl uptake would be acutely elevated in unilateral ankle sprain and if tracer uptake would be reduced as a function of healing, and correlated with pain localizations and pain experience.
Methods: Eight otherwise healthy patients with unilateral ankle sprain were recruited at the emergency department. All underwent [^{11}C]-D-deprenyl PET/CT in the acute phase, at one month and 6–14 months after injury.

Abbreviations: PET, positron emission tomography; PET/CT, positron emission tomography/computed tomography; MAO, monoamine oxidase; [^{11}C]DDE, [^{11}C]-D-deprenyl; ACP, acute phase; FU1, first follow-up; FU2, second follow-up; VAS, visual analogue scale; SUV, standardized uptake value; ROI, region of interest; VOI, volume of interest; TACT, time activity; FTA, anterior fibulotalar ligament.

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Results: Acute [^{11}C]-D-deprenyl uptake at the injury site was a factor of 10.7 (range 2.9–37.3) higher than the intact ankle. During healing, [^{11}C]-D-deprenyl uptake decreased, but did not normalize until after 11 months. Patients experiencing persistent pain had prolonged [^{11}C]-D-deprenyl uptake in painful locations.
Conclusions and implications: The data provide further support that [^{11}C]-D-deprenyl PET can visualize, quantify and follow processes in peripheral tissue that may relate to soft tissue injuries, inflammation and associated nociceptive signaling. Such an objective correlate would represent a progress in pain research, as well as in clinical pain diagnostics and management.

1. Introduction

Pain is a uniquely personal experience, and self-reports remain the gold standard of assessment. However, self-reports are affected by numerous factors [1]. Objective visualization and quantification of peripheral musculoskeletal injury that generates nociceptive input would represent a progress in pain research. The visualization of pain-associated processes in peripheral tissue would facilitate diagnosis, strengthen patients' self-report and aid clinical decisions. Further quantification of nociception related processes in peripheral tissue would guide clinical assessment and treatment monitoring.

Positron emission tomography (PET) is increasingly used to diagnose, characterize and monitor disease activity in peripheral inflammatory disorders of both known and unknown origin [2,3]. Nociceptive pain is a cardinal feature of inflammation, and although tissue injury that induces inflammation plays a pivotal role in the generation of pain [4], few studies have localized and quantified the extent of peripheral injury and inflammation in pain patients with molecular imaging.

[^{11}C]-D-deprenyl (D-[N-methyl-11C]N, N-methyl, propargylamphetamine) is the D-isomer of deprenyl, a well-characterized monoamine oxidase-B (MAO-B) inhibitor with anti-inflammatory and neuro-protective properties. Based on the available data D-deprenyl binds to MAO enzymes located in the outer mitochondrial membrane of cells engaged in processes involved in inflammation and repair [5]. Previous PET studies have shown high and irreversible [^{11}C]-D-deprenyl ([^{11}C]DDE) uptake in synovial inflammation of knees in rheumatoid arthritis patients [6] and in patients with chronic whiplash associated disorder [^{11}C]DDE uptake was increased in the painful neck regions [7]. These studies strongly suggest an association of [^{11}C]DDE uptake in soft tissue injury and inflammation with associated pain. However, it is not known if [^{11}C]DDE PET can indicate acute tissue damage and pain, and if the healing process can be followed over time in the setting of acute injury. The purpose of this study was to verify and extend previous [^{11}C]DDE-PET findings by investigating tracer retention in unilateral ankle sprain. Traumatic ankle sprain presents a suitable model with substantial pain in the acute phase and reasonably rapid resolution of pain within months. With isolated traumatic ankle sprain, the intact ankle can be used as a within-subject non-affected control. The hypotheses were that [^{11}C]DDE uptake would be acutely elevated localized to injured tissues, reduced as a function of healing, and correlated with subjective pain localizations and pain experience.

2. Materials and methods

2.1. Patients and study design

Eight non-smoking patients with an acute isolated traumatic ankle sprain, diagnosed by an orthopedic surgeon, were recruited at the emergency department at Uppsala University Hospital, Uppsala, Sweden. No patient had a history of a somatic or psychiatric disease or drug abuse.

The study design consisted of three [^{11}C]DDE PET/CT investigations on both ankles of each patient. The first imaging occasion (acute phase; ACP) was scheduled within 5 days after the injury. The first follow-up imaging occasion (FU1) was scheduled 6 ± 1 weeks after the injury in order to monitor the subacute or repair phase of the tissue injury. The second follow-up (FU2) was scheduled 6 ± 1 months after the injury in order to monitor the remodeling phase of the tissue injury. During the course of the study it was noticed that complete healing and recovery of the injured peripheral tissue might take longer time than expected. Therefore, three of the patients had their FU2 imaging between 9 and 14 months after the injury. Before each PET/CT investigation, all patients refrained from analgesics and anti-inflammatory drugs for 24 h, from alcohol and caffeine for 12 h, and from food for 3 h.

2.2. Pain assessment

Immediately before and after PET/CT investigations, patients rated their average resting pain levels in the feet on a visual analogue scale (VAS), ranging from 0 (no pain) to 10 (worst imaginable pain). The locations of maximal tenderness were palpated and marked on an anatomical picture of the foot. The patient characteristics are presented in Table 1.

2.3. PET/CT scanning

The radioligand [^{11}C]DDE was produced at the chemistry section of the Uppsala PET center according to a standard manufacturing procedure with previously published methods [8,9]. All patients were investigated with a GE Discovery ST PET/CT scanner (General Electric Medical Systems, Milwaukee, WI, USA). The scanner provides 47 contiguous planes of data with a distance of 3.27 mm and 3.125 mm transaxial and axial resolution: this gives a total axial field of 15.7 cm. Patients were scanned in the supine position with the feet gently supported by a vacuum cushion to minimize foot and ankle movement. The PET/CT investigation was initiated with a short CT scan (140 kV; auto mA 10–80 mA) for attenuation correction of the PET emission data. Each patient received an intravenous bolus of approximately 5 MBq/kg [^{11}C]DDE in an antecubital vein. Simultaneously, a dynamic emission scan (3D mode) was initiated with a predetermined set of measurements (frames of 4×30; 3×60; 2×300, and 3×600 s) for up to 45 min. PET data were reconstructed with the OSEM (Ordered Subset Expectation Maximization) algorithm with 2 iterations and 21 subsets and with a 2.57 mm wide post-processing filter. PET data were corrected for decay, photon attenuation, scatter, random coincidences and dead time.

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