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Quantification of opioid receptor availability following spontaneous epileptic seizures: Correction of [^{11}C]diprenorphine PET data for the partial-volume effect

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ABSTRACT

Previous positron emission tomography (PET) studies in refractory temporal lobe epilepsy (TLE) using the non-selective opioid receptor antagonist [^{11}C]diprenorphine (DPN) did not detect any changes in mesial temporal structures, despite known involvement of the hippocampus in seizure generation. Normal binding in smaller hippocampi is suggestive of increased receptor concentration in the remaining grey matter. Correction for partial-volume effect (PVE) has not been used in previous DPN PET studies. Here, we present PVE-corrected DPN-PET data quantifying post-ictal and interictal opioid receptor availability in humans with mTLE.

Eight paired datasets of post-ictal and interictal DPN PET scans and eleven test/retest control datasets were available from a previously published study on opioid receptor changes in TLE following seizures (Hammers et al., 2007a). Five of the eight participants with TLE had documented hippocampal sclerosis. Data were re-analyzed using regions of interest and a novel PVE correction method (structural functional synergistic-resolution recovery (SFS-RR); (Shidahara et al., 2012)). Data were denoised, followed by application of SFS-RR, with anatomical information derived via precise anatomical segmentation of the participants' MRI (MAPER; (Heckemann et al., 2010)). [^{11}C]diprenorphine volume-of-distribution (V_T) was quantified in six regions of interest.

Post-ictal increases were observed in the ipsilateral fusiform gyri and lateral temporal pole. A novel finding was a post-ictal increase in [^{11}C]DPN V_T relative to the interictal state in the ipsilateral parahippocampal gyrus, not observed in uncorrected datasets. As for voxel-based (SPM) analyses, correction for global V_T values was essential in order to demonstrate focal post-ictal increases in [^{11}C]DPN V_T.

This study provides further direct human *in vivo* evidence for changes in opioid receptor availability in TLE following seizures, including changes that were not evident without PVE correction. Denoising, resolution recovery and precise anatomical segmentation can extract valuable information from PET studies that would be missed with conventional post-processing procedures.

Introduction

The opioid peptide receptor (OPR) system comprises μ (MOP), δ (DOP), κ (KOP) and nociceptin/orphanin FQ (NOP; also known as ORL-1) opioid peptide receptors (for review: (Dhawan et al., 1996; Satoh and Minami, 1995)), which bind endogenous opioids known as enkephalins and endorphins. The receptors are coupled to G-protein, and have seven transmembrane domains (Chaturvedi et al., 2000).

Abbreviations: [^{11}C]DPN, [^{11}C]diprenorphine; DOP, δ opioid peptide; KOP, κ opioid peptide; HS, hippocampal sclerosis; MAPER, multi-atlas propagation using enhanced registration; MOP, μ-opioid peptide; MR, magnetic resonance; OPR, opioid peptide receptor; PVE, partial volume effect; SFS-RR, structural functional synergistic-resolution recovery; TLE, temporal lobe epilepsy; V_T, volume-of-distribution.

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There is growing evidence for an anticonvulsant action of these endogenous peptides, in a 'tonic antiepileptic' system that is hypothesized to limit the spread of electrical activity within the temporal lobe (Hammers et al., 2007a; Koepp and Duncan, 2000; Mayberg et al., 1991). The most convincing evidence implies a role for opioid peptides in post-ictal seizure inhibition (Engel et al., 1981; Pirker et al., 2009). It remains difficult to ascribe this to a single opioid receptor subtype; recent work in prodynorphin knockouts implicates the kappa receptor (Loacker et al., 2007), whereas activation of the mu-opioid receptor has a 'bi-directional' influence (for review: (Tortella, 1988)).

PET studies of opioid-receptor mediated neurotransmission in epilepsy have provided evidence for a dynamic relationship between opioid peptide receptor availability and seizures (for review: (Hammers and Lingford-Hughes, 2006)). Interictal studies suggest increased MOP and DOP receptor availability in the ipsilateral temporal lobe during the interictal period in temporal lobe epilepsy (TLE; (Frost et al., 1988; Madar et al., 1997; Mayberg et al., 1991)). Ictal studies of reading-induced and absence epilepsies suggest decreased opioid MOP-, DOP- and KOP-receptor availability during seizures (Bartenstein et al., 1993; Koepp et al., 1998). Post-ictal opioid peptide receptor availability is increased in the ipsilateral temporal lobe in TLE (Hammers et al., 2007a).

All PET studies to date have failed to demonstrate or explicitly document significant alteration of hippocampal or parahippocampal gyrus opioid peptide receptor binding (interictal or post-ictal) in TLE (for review (Hammers and Lingford-Hughes, 2006)). This is surprising, given the association of these regions with TLE. The finding of apparently normal opioid peptide receptor availability in sclerotic hippocampi suggests that the opioid binding per neuron is actually upregulated in these regions. Recently, increased hippocampal mu-opioid receptor mRNA expression and G-protein binding was documented in humans with refractory TLE *ex vivo* (Cuellar-Herrera et al., 2012). It should be noted that radioligands such as [^{11}C] diprenorphine are not subtype-selective, and so density alterations of the different subtypes in opposing directions could cancel each other out when ligand binding is being measured. However, the possibility that failure to detect hippocampal or parahippocampal alterations is the result of the limited resolution of the PET system and associated partial-volume effect (PVE) has not been assessed.

The PVE consists of the blurring of focal PET activity distribution by a 'point-spread function' due to suboptimal camera resolution with consequential signal 'spill out' into surrounding regions. A consequence of this 'intensity diffusion' is the under- and over-estimation of regional concentrations of radioactivity (Aston et al., 2002; Meltzer et al., 1996).

Intensity diffusion is of particular relevance to studies of temporal lobe epilepsy. Regions of interest such as the hippocampi, parahippocampal gyri, and amygdalae are small structures. This problem is exacerbated by the volume loss of mesial temporal sclerosis that is frequently observed in TLE, an effect that is not limited to the hippocampi, and may be bilateral. For example, gliosis and neuronal loss in the amygdala ('amygdala sclerosis') has been reported in isolation and also in 35–76% of patients with hippocampal sclerosis (HS) at post-mortem ((ILAE Commission on Neurosurgery of Epilepsy, 2004; Yilmazer-Hanke et al., 2000)). Volume loss in the parahippocampal gyrus is also recognized (Bernasconi et al., 2003). The accuracy of quantification of the activity from such regions is therefore decreased, as the activity from anatomically smaller regions is underestimated in a non-linear fashion (Hoffman et al., 1979).

'Structural functional synergistic-resolution recovery' (SFS-RR; (Shidahara et al., 2009, 2012)) is a novel partial-volume effect correction method that has been evaluated in simulations and in human [^{18}F]FDG and [^{11}C]raclopride PET studies. The model is flexible in that the reliance upon structural data is varied relative to the quality of anatomical detail (for example, MRI data is weighted more strongly than CT data). The method uses the wavelet transform (WT) (Mallat, 1989; Turkheimer et al., 1999) to decompose the functional images (such as PET) and structural reference image (such as MRI) into several resolution elements. The high-resolution component of the PET image is then replaced with the scaled structural image, based on the assumption that the conventional PET image does not have enough high-resolution components. To suppress distribution mismatch between functional and anatomical images, an individualized frequency based atlas (Hammers et al., 2003) was used as the structural reference image in the validation studies. The authors demonstrated that the use of such an atlas outperforms the use of CT/MRI data alone (Shidahara et al., 2009).

Here we describe the application of SFS-RR, enhanced with more accurate automated as well as manual region definitions, to the data acquired by (Hammers et al., 2007a,b) for the accurate quantification of [^{11}C]DPN binding in regions vulnerable to intensity diffusion. Our objective was to accurately quantify post-ictal and interictal opioid receptor binding in participants with refractory TLE, in order to correlate clinical variables with the correctly quantified opioid binding per unit of grey matter.

Our primary hypothesis was that decreased interictal [^{11}C]DPN V_T would be evident in the sclerotic hippocampus of participants whose TLE is associated with HS. Our secondary hypothesis was that increased post-ictal [^{11}C]DPN V_T would also be evident in mesial temporal structures, in addition to our previous finding of post-ictal increases in [^{11}C]DPN V_T in the extra-mesial ipsilateral temporal lobe in PVE-uncorrected data.

Material and methods

The datasets for this study had been previously acquired for another study, which did not use PVE correction. Details of participants' demographics and clinical data, PET and other data acquisition have been described in detail elsewhere (Hammers et al., 2007a,b). Briefly, for re-analysis eight participants with refractory TLE (four males; median age 45.5 years, range 32–60 years) who were scanned interictally, and also post-ictally within 22 h (median 10.0 h, range 1.5–21.3 h) after spontaneous temporal lobe seizures were available. The diagnosis of TLE was based on history, seizure semiology, interictal EEG features and neuropsychological examination. The lateralization of TLE was additionally based on MRI findings and ictal EEG (when available; seven of eight participants, including all 'MRI-normal' participants). One of the original nine participants with refractory TLE (number 5) was excluded from re-analysis due to irretrievable loss of MRI data. Eleven healthy controls (eight males; median age 42.0 years, range 30–58 years) had been scanned twice under the same conditions.

PET data acquisition and analysis

Images had been acquired using a Siemens/CTI ECAT EXACT3D 966 PET camera over 90 min, subsequent to injection of a median dose of 185 MBq (range 130–200 MBq) of [^{11}C]DPN. 3D Volumetric T1-weighted MRI scans were acquired for co-registration with the PET dataset using a 1.0 T Picker HPQ scanner (Robert Steiner MRI unit, Hammersmith Hospital; voxel sizes 1 mm × 1 mm × 1.3 mm) or a 1.5 T General Electric Signa Echospeed scanner (National Society for Epilepsy; voxel sizes 0.9375 mm × 0.9375 mm × 1.5 mm).

Derivation of individual arterial plasma input functions corrected for metabolism has been described elsewhere (Hammers et al., 2007a,b). Briefly, continuous (first 15 min) and discrete arterial blood sampling was used to determine the partition of radioactivity and the parent fraction (Luthra et al., 1993).

Dynamic images, metabolite-corrected arterial plasma input functions (COMIF; in-house software), and spectral analysis (Cunningham and Jones, 1993) implemented in RPM (Turkheimer et al., 2003) (Gunn et al., internal software), were used to create voxel-by-voxel parametric images of [^{11}C]DPN volume-of-distribution (V_T) as previously described (Hammers et al., 2007b).