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Review

Imaging central neurochemical alterations in chronic pain with proton magnetic resonance spectroscopy

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ABSTRACT

Proton magnetic resonance spectroscopy has been used extensively in the study of various neurobiological disorders: depression, schizophrenia, autism, etc. But its application to chronic pain is relatively new. Not many studies in chronic pain have used ^{1}H-MRS. The unique ability of ^{1}H-MRS to assess both static and dynamic levels of glutamate and γ-aminobutyric acid (GABA) gives this method a unique position in neuroscience. Emerging evidence in chronic pain suggests an elevated excitatory/inhibitory neurotransmitter ratio is present within brain regions involved in pain processing. The combination of ^{1}H-MRS imaging with pharmacologic interventions holds significant promise as a direct one-to-one matching of disease pathology with drug mechanism of action can be made. As such ^{1}H-MRS may be useful in discovery of novel compounds for chronic pain. Research in these areas may lead to improved diagnosis and treatment of these complex patients.

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There has been tremendous progress in our understanding of the spinal and supraspinal mechanisms involved in pain transmission over the past two decades. Some of these insights were gained from preclinical studies that examined the precise cellular and molecular processes and pathways involved in acute pain transmission and in animal models of chronic pain. But many of the advances in the pain field have occurred because of our improved ability to study pain mechanisms in humans. Functional magnetic resonance imaging (fMRI) in particular has had a tremendous impact on the localisation and understanding of brain regions involved in pain perception, as evidenced by the articles in this special edition. FMRI has advantages over techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) in that it does not require the administration of radioactive substances and it has good temporal and spatial resolution. However both structural and functional MRI suffer from significant limitations. The exact relationship between neural activity and changes in the blood oxygenation level dependent (BOLD) signal remain somewhat unknown [24], and structural and functional MRI provide little or no information with respect to the types of neurotransmitters and receptors that underlie neuronal activity. These limitations have implications for how well any given neuroimaging technique can assist in the development of novel treatments (see below). Even with receptor PET, which can assess the release of some neurotransmitters [47], currently there are no available radio tracers that are sensitive to changes in the brain's two primary signalling molecules: glutamate and γ-aminobutyric acid (GABA). Although a PET radio ligand exists for the metabotropic glutamate receptor subtype 5 [5], it is not clear if changes in receptor binding with this ligand ([^{11}C]ABP688) reflect changes in glutamate extracellular concentrations. In this respect, neurochemical imaging techniques such as proton magnetic resonance spectroscopy (^{1}H-MRS) have begun to show promise.

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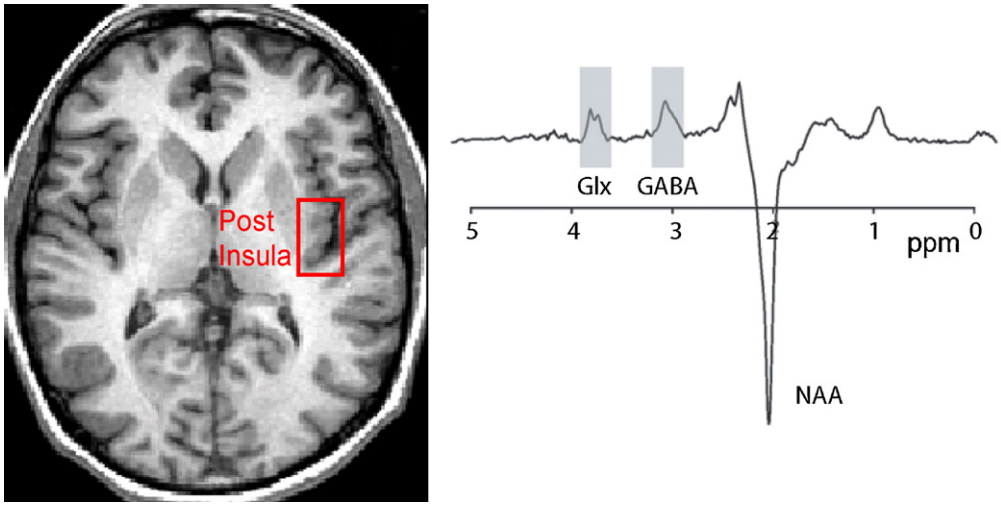

Fig. 1. Representative ^{1}H-MRS voxel placement and resulting spectrum for the posterior insula. Axial T1-weighted image showing single-voxel placement for the right posterior insula (left) with resulting proton magnetic resonance spectroscopy spectrum (right) using the MEGA-PRESS editing technique. Glx is resolved at 3.8 ppm, GABA at 3.0 ppm, and an inverted NAA peak at 2.0 ppm.

1. Proton magnetic resonance spectroscopy (^{1}H-MRS)

^{1}H-MRS is a non-invasive MRI technique that can quantify the concentration of multiple metabolites, including glutamate and GABA, within the living human brain. Rather than obtaining a spatial map of brain activity over time, as in traditional fMRI, this technique generates a chemical specific spectrum by exciting protons with characteristic resonance frequencies (see Fig. 1) [4]. ^{1}H-MRS methods are amenable to both cross-sectional as well as longitudinal studies, as specific regions of interest can be identified between subjects as well as within the same participant over time. Once ^{1}H-MRS spectra are acquired, they can be analyzed to determine the relative concentrations of different central nervous system metabolites. Historically these metabolites have been: N-acetyl-aspartate (NAA), choline (Cho), and creatine (Cr) as these molecules displayed a good signal to noise ratio [4,35]. Abnormalities in the concentrations of these metabolites have been associated with various pathological changes in the underlying brain tissue. NAA is generally believed to be a marker of neuronal density and viability, as lower concentrations of this metabolite are thought to be indicative of loss of neural function [28,36]. Cho is a considered a marker of membrane integrity and altered levels of this molecule are also associated with neurobiological diseases [36]. Cr reflects ATP metabolism and production and is relatively constant across the brain. Because of its relative stability across brain regions, it is sometimes used as a reference metabolite to which other species are normalized to.

^{1}H-MRS has been used widely in brain disorders such as depression [45], bipolar disorder [44], schizophrenia [2,26], and epilepsy [20]; however, the application of ^{1}H-MRS to the investigation of chronic pain has been slow in coming. Grachev et al. was the first to discover lower NAA levels within the dorsolateral prefrontal cortex (DLPFC) of individuals with chronic low back pain as compared to healthy controls [15]. Subsequent reports of lower brain NAA levels have also been found in other chronic pain conditions. Low levels of thalamic NAA have been reported in neuropathic pain [13,32] and trigeminal neuralgia [16], and similar findings, albeit in other brain regions, have been observed in headache and migraine [6,42]. These NAA findings seem to be consistent across pain disorders suggesting a common chemical alteration in chronic pain. However at this point we do not know if lower NAA is a cause or a consequence of having pain because longitudinal studies are needed to examine this relationship. Although no current consensus has been reached regarding reduced NAA levels in chronic pain, it may reflect a down regulation of neuronal activity which may be a precursor or a result of neuronal damage. Our group has also found an association with Cho levels within the DLPFC of chronic pain patients diagnosed with fibromyalgia (FM), wherein Cho levels were positively correlated with chronic pain report [33]. While these findings of altered NAA and Cho are intriguing, the precise roles of these metabolites in brain function are somewhat uncertain. It is not at all clear how alterations in these metabolites contribute to chronic pain.

2. ^{1}H-MRS derived glutamate levels in chronic pain

Recent ^{1}H-MRS research has begun to explore the role of brain glutamate in chronic pain patients. This research has lagged behind the studies examining NAA and Cho because of the increased inherent difficulty in obtaining spectra for glutamate. For example glutamate resonances overlap at 3 T with glutamine, making it difficult to quantify glutamate levels in isolation [4]. As such it is common for investigators to report the combined levels of glutamate and glutamine, termed Glx, in addition to reporting these metabolites in isolation.

Glutamate is the brain's main excitatory neurotransmitter and it exerts its effects *via* binding to both ionotropic and metabotropic receptors [22]. Ionotropic receptors are ligand-gated ion channels generally involved in fast synaptic transmission, which open up permeation pathways through the plasma membrane allowing for fast changes in membrane potentials. Metabotropic receptors are G-protein coupled receptors that signal through cytoplasmic second messengers and are more involved in modulation of neural activity. We have known for some time that glutamatergic neurotransmission plays a key role in pain. For example the development of neuropathic pain in preclinical models is thought to be in part a result of central sensitization, or central plasticity, involving both ionotropic as well as metabotropic glutamate receptors (for review see [23]). Although it remains to be seen if processes such as central sensitization are also involved in plastic changes within the brains of chronic pain patients, newer ^{1}H-MRS studies are suggesting altered glutamatergic activity in these patients.

Our group was the first to use ^{1}H-MRS to study glutamate and Glx levels specifically in patients with chronic "centralized" pain such as fibromyalgia (FM). In a longitudinal trial, we demonstrated that FM patients display significant correlations between changes in glutamate (and Glx), within the posterior insula cortex,