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Neurochemical changes in patients with chronic low back pain detected by proton magnetic resonance spectroscopy: A systematic review

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ABSTRACT

Background: Low back pain is a highly prevalent health problem around the world, affecting 50% to 85% of people at some point in life. The purpose of this systematic review is to summarize the previous proton magnetic resonance spectroscopy studies on brain chemical changes in patients with chronic low back pain (CLBP).
Methods: We identified relevant studies from a literature search of PubMed and EMBASE from 1980 to March 2016. Data extraction was performed on the subjects' characteristics, MRS methods, spectral analyses, cerebral metabolites and perceptual measurements.
Results: The review identified 9 studies that met the inclusion criteria, comprised of data on 135 CLBP subjects and 137 healthy controls. Seven of these studies reported statistically different neurochemical alterations in patients with CLBP. The results showed that compared to controls, CLBP patients showed reductions of 1) *N*-acetylaspartate (NAA) in the dorsolateral prefrontal cortex (DLPFC), right primary motor cortex, left somatosensory cortex (SSC), left anterior insula and anterior cingulate cortex (ACC); 2) glutamate in the ACC; 3) myo-inositol in the ACC and thalamus; 4) choline in the right SSC; and 5) glucose in the DLPFC.
Conclusion: This review provides evidence for alterations in the biochemical profile of the brain in patients with CLBP, which suggests that biochemical changes may play a significant role in the development and pathophysiology of CLBP and shed light on the development of new treatments for CLBP.

Contents

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1. Introduction

Low back pain (LBP) is a highly prevalent health problem around the world (Kamper et al., 2015), affecting 50% to 85% of people at some point in life (Becker et al., 2010). According to the Global Burden of Disease Study in 2013, LBP ranked first in the top ten causes of years lived with disability (YLDs) (Vos et al., 2015). When LBP persists for >-6 months (Koes et al., 2006; Van Tulder et al., 2003), it is classified as chronic low back pain (CLBP), which leads to considerable health care costs (Dagenais et al., 2008). Since the precise causes and origins of CLBP are unknown to 90% of patients (Koes et al., 2006), therapeutic methods targeting LBP symptoms are often nonspecific and ineffective.

Recently, neuroimaging techniques have been used to advance our understanding of back pain mechanisms (Giesecke et al., 2004; Kobayashi et al., 2009; Lloyd et al., 2008). In vivo magnetic resonance spectroscopy (MRS) is a non-invasive brain imaging method that can explore metabolic concentrations within certain brain regions. MRS detects radiofrequency signals generated by the magnetic nuclear spins of magnetically active nuclei such as protons, phosphorus, carbon and fluorine, which are excited by external magnetic fields (Glunde and Bhujwalla, 2011; Glunde et al., 2011). Compared with other nuclei, proton nuclei (^{1}H) are widely used in MRS studies because of their high magnetic sensitivity and natural abundance in tissues (Bulik et al., 2013; Soares and Law, 2009). Another benefit of in vivo ^{1}H MRS is that it can be conducted in clinical MRI scanners without any additional hardware (Malet-Martino and Holzgrabe, 2011).

Unlike traditional functional MRI, which obtains a spatial map of brain activity, ^{1}H MRS voxel placement generates a graphical spectrum of specific regions of the brain (Harris and Clauw, 2012). The peaks on the spectra represent various cerebral metabolites, including *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (mI), glutamate (Glu), glutamine (Gln), gamma-aminobutyric acid (GABA) and glucose (Glc). Concentration changes of these metabolites are associated with numerous neurological diseases (Aguila et al., 2015; Bustillo et al., 2010; Vrenken et al., 2005), and can sometimes be detected prior to the onset of symptoms (Godbolt et al., 2006).

Over the past two decades, a growing number of proton magnetic resonance spectroscopy (^{1}H MRS) studies have been applied to investigate biochemical changes in individuals with CLBP. Although results from these studies have shown that CLBP patients exhibit altered ^{1}H MRS signal changes in different brain regions, some of the results obtained appear contradictory. Therefore, we performed this systematic review of previous ^{1}H MRS studies on CLBP to summarize the biochemical changes in brain regions of interest and to explore potential reasons for those inconsistent findings.

2. Material and methods

We conducted a systematic search of published studies in PubMed and EMBASE from 1980 to March 2016. The Medical Subject Headings were “magnetic resonance spectroscopy” and “back pain”. The search strategy also included key words such as “magnetic resonance spectroscopy”, “MRS”, “spectroscopy” and “back pain” to identify relevant studies. No language restrictions were applied. The reference lists of the selected articles were also reviewed to search for additional relevant studies. The protocol for this review was registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO; CRD42016045845).

Titles and abstracts of potentially relevant studies were examined to determine whether they fulfilled the following inclusion criteria: (1) Studies compared LBP patients with healthy controls, and (2) studies employed ^{1}H MRS to measure metabolite concentrations in the brain. We excluded studies that (1) did not present original data, and (2) did not recruit LBP patients. After reviewing the full texts, one study was excluded because half of the patients in the study did not present with low back pain symptoms.

Data extraction was performed for subject and control numbers, gender, age, diagnostic tools, duration of LBP symptoms, comorbidities with LBP, medications, clinical measurements, metabolites studied, brain regions of interest, voxels of interest, MR scanner devices, magnetic field strengths, MRS sequences, repetition times, echo times, spectral analysis software, metabolite quantification methods (absolute quantification or ratios to Cr), and data inclusion criteria.

3. Results

Our literature search yielded 271 potentially relevant studies on patients with CLBP and healthy controls. 262 studies were excluded for reasons listed in Fig. 1. Tables 1 and 2 and Fig. 2 summarize the characteristics of the 9 included studies.

3.1. Subjects

The 9 studies recruited a total of 135 CLBP subjects and 137 healthy controls. All of the studies except for one study (Siddall et al., 2006) reported subject numbers by sex, which showed that the majority of subjects were females. For diagnosis of CLBP, three of the included studies adopted the diagnostic criteria of Merskey and Bogduk (Grachev et al., 2000, 2002, 2003), and two studies utilized classification from the International Association for the Study of Pain (Grachev et al., 2002; Siddall et al., 2006). All of the patients presented with LBP for >6 months.

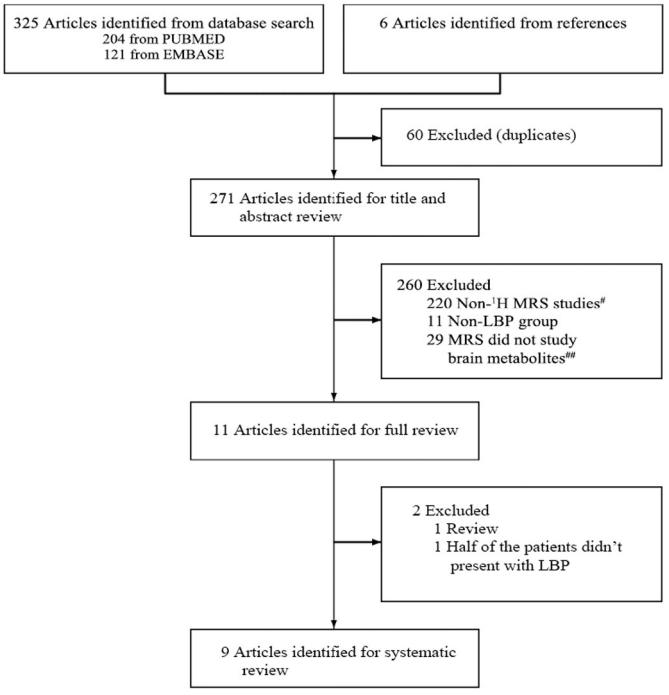

Fig. 1. Flow diagram of search strategy. #220 publications were excluded because they were near-infrared spectroscopy, atomic spectroscopy, 31P MRS studies and so on. ##These 29 studies mainly focused on concentrations of metabolites in the spinal cord, paraspinal muscles and intervertebral discs of LBP patients.