N-acetyl-aspartate (NAA) as a correlate of pharmacological treatment in psychiatric disorders: A systematic review

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Abstract
The amino-acid N-acetyl-aspartate (NAA) is located in neurons and the concentration of NAA correlates with neuronal mitochondrial function. The signal of NAA, as measured with proton magnetic resonance spectroscopy (1H-MRS), is considered to reflect both, neuronal density and integrity of neuronal mitochondria. A reduction of the NAA concentrations has been found in several psychiatric disorders. Newer studies report reversal of decreased NAA concentration with treatment. The objective of this review is to summarize the literature on NAA changes in association with psychopharmacological treatment in psychiatric disorders (affective disorders, obsessive-compulsive disorder, schizophrenia and dementia). The majority of studies identified increased NAA concentrations in response to treatment, while a smaller number of studies did not find this effect. The NAA increase seems to be neither specific for a certain disorder nor for a specific intervention. This suggests that the reduction of NAA may represent an altered functional (metabolic) state of neurons common to different psychiatric disorders and the increase after treatment to indicate functional restoration as one general effect of interventions.

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1. Introduction
Effects of psychiatric interventions are measured with scales for clinical signs and symptoms of the respective disorder. This approach targets relevant endpoints, but fails to capture biological effects of interventions. Biological
treatment markers are crucial to (1) improve the understanding of treatment effects on disease mechanisms, (2) to assess treatment effects independent of clinical ratings and (3) to predict clinical response to treatment. Biomarkers for this purpose are increasingly developed and incorporated in clinical trials in various psychiatric disorders.

Magnetic resonance (MR) brain imaging technologies are particularly suitable for application in clinical trials as they are non-invasive, safe, free of radiation, repeatable, and widely available. MR spectroscopy (MRS) provides information on the biochemical composition of brain tissue. Proton MRS (1H-MRS) detects the resonance of protons within water. In addition, it detects proton resonance in other distinct molecules due to slight modifications of the resonance frequencies by the respective local molecular configuration (“chemical shift”). The areas under different peaks of 1H-MRS spectrum are proportional to the number of signal-generating protons of these molecules. Most commonly, 1H-MRS is performed as single-voxel spectroscopy, where a spectrum is obtained from a specific target area in the brain covered by one voxel (e.g. hippocampus) (Figure 1A). In contrast, MR spectroscopic imaging (MRSI) provides metabolic maps indicating regional concentration of different molecules (Figure 1B). (Brown, 1992; Maudsley et al., 1994)

The most prominent signal obtained with 1H-MRS in humans reflects the concentration of the amino-acid N-acetylaspartate (NAA) (peak at about 2.02 ppm relative to the reference tetramethylsilane, TMS) (Figure 1). The stability of the NAA signal is high with a test-retest variation around 5% in healthy humans (Schirmer and Auer, 2000). Multicenter stability of the NAA signal has also been demonstrated (Träber et al., 2006). NAA is highly concentrated in neurons (around 7.1 mmol/kg) (Urenjak et al., 1992; Clark, 1998). The NAA concentration obtained by 1H-MRS correlates with neuronal density and neuronal damage in post mortem studies (Cheng et al., 1997; Lentz et al., 2005). The functional role of NAA in neurons is not fully resolved. There is evidence of involvement of NAA in osmoregulation, myelin synthesis and neuron-glia signaling as well as turnover of N-acetylaspartylglutamic (NAAG) and glutamate (Baslow, 2003; Moffett et al., 2007). The metabolism of NAA is well characterized. It is synthesized mainly in the mitochondria of neurons from aspartate and acetyl-CoA (Arun et al., 2009). From there, NAA is transported into the neuronal cytoplasm and eventually transferred to oligodendrocytes from degradation into aspartate and acetate (Baslow, 2010). The synthesis of NAA is closely coupled with the functional integrity of neuronal mitochondria and the concentration of NAA corresponds to neuronal energy consumption (Clark, 1998; Moffett et al., 2007). Thus, NAA may serve as a non-invasive brain imaging marker of the functional status of neuronal mitochondria in addition to being a marker of neuronal density.

A high number of 1H-MRS studies demonstrated decreased NAA concentration in psychiatric conditions, including affective

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