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A role for bioenergetic abnormalities in the pathophysiology of schizophrenia

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Schizophrenia (SZ) is a common and severe psychiatric disorder but its pathophysiology is poorly understood. Outcomes in SZ may improve significantly with early intervention (1). But how should we intervene in the critical physiological changes in early SZ? There is strong evidence for NMDA receptor hypofunction and abnormal glutamatergic neurotransmission in SZ, which in turn is leads to neurodegenerative features such as dendritic dysgenesis and reduced spine density (2-4). These abnormalities may play a role in neurodevelopmental alterations (5) and lead to GABAergic dysfunction (6). This evidence and the increasing availability of glutamatergic agents make glutamate signaling an attractive target in SZ (7-8). Neuroimaging studies indicate overactive glutamate signaling in first episode SZ which "burns out" with transition to chronic disease, as other (possibly downstream) changes such as cortical thinning (9) and cognitive impairment emerge. Our group's research has focused on neurotransmission and information processing in psychosis, probing many of the processes described above (10). In this editorial, I will present one aspect of this work, specifically relating to brain energy metabolism.

Glutamate signaling is an energy-intensive process and there is coupling between this process and brain energy utilization in the awake resting human cerebral cortex (11-13). Thus, supporting glutamatergic neurotransmission appears to be one of the main functions for the brain's energy production machinery (14). In fact, energy utilization is related to glutamate signaling in an almost one-to-one fashion. Therefore, abnormalities in underlying energy metabolism could play a major role in the abnormalities seen in glutamate signaling in SZ.

Bioenergetic activity in the brain includes a complex network of brain metabolic and hemodynamic processes, including glucose oxidation, ATP generation through the ATPase enzyme inside mitochondria, and ATP utilization (mainly in the cytosol). ATP utilization is the primary driving force for most processes inside a cell, including enzymatic reactions, transport of materials, and DNA and RNA synthesis. In neurons, the majority of energy generated in mitochondria is used to maintain Na^+/K^+ ion gradients across the cell membrane as part of glutamate signaling (15-16). This requires energy transport between mitochondria and cytosol. This is accomplished by phosphocreatine (PCr) through reversible creatine kinase (CK) reactions. When new ATP is synthesized, it transfers a phosphate moiety to PCr, which diffuses around the cell to locations where ATP is required. At the site where ATP is required, PCr transfers the phosphate moiety back to ADP to generate ATP which is then utilized as needed. Thus, PCr helps maintain a stable brain ATP level (17-19). There are two coupled CK reactions: one occurring in the mitochondrial intermembraneous space and another in cytosol. During functional brain activation cellular ATP levels remain stable as new ATP is synthesized from PCr. Because the CK reaction is reversible, PCr is reduced when ATP is being generated at the site of need, but then it is replenished when energy balance is restored and new ATP is no longer needed (19). Therefore, the CK reaction rate reflects the cell's ability to maintain ATP levels during times of high energy demand. The ATPase reaction, by contrast, reflects mitochondria-specific ATP synthesis de novo.

There is extensive evidence for abnormalities in brain bioenergetics in SZ, including PET studies of cerebral glucose utilization (20), 31P MRS studies of high energy phosphate (HEP) molecules (21-22), and postmortem studies of bioenergetics-related gene expression (23-24). In previous work, we reported that the concentration of total Cr (tCr - including Cr and PCr) is reduced in the anterior cingulate and parieto-occipital cortex of patents with SZ using 1H-MRS (22). More recently, we

developed a 31P magnetization transfer (MT) MRS approach to dynamically quantify reaction rates of ATPase and CK in addition to steady-state concentrations of HEP molecules such as ATP and phosphocreatine (PCr) (25-26). Steady state concentrations of metabolites reflect a final pathway where abnormalities may become manifest, but it is possible that enzymatic reactions in a cell are slowed but metabolite levels remain normal at baseline. This would mask any abnormalities, requiring dynamic measures such as 31P MT MRS to address the issue.

31P MT MRS involves suppression of signal from one resonance (e.g. ATP) using a radiofrequency pulse. Resonances which are in chemical exchange with the suppressed one (e.g. PCr) are then attenuated in proportion to the reaction rate (e.g. of CK). As discussed further below, we have used this approach to document bioenergetic compromise in the prefrontal cortex in chronic SZ. Since there is reduced CK activity but normal PCr and ATP concentrations in SZ, it appears that brain bioenergetics at rest is in a "distressed but compensated" state (27). Additional cell biology and gene expression studies are consistent with this statement (24,28-31). Unfortunately, the remainder of the bioenergetics MRS literature in SZ contains multiple discrepancies. Cr and HEP steady-state concentrations have been reported as increased, decreased, or normal (32-39). These discrepancies may be due to differences in methodology, patient characteristics, and medication effects (40-42). We will not go into this literature any further here, but it is critical to carry out new studies with high quality data in well-defined patient populations to resolve these discrepancies.

Our recent report is exciting but multiple questions remain unanswered about bioenergetics in SZ. First, there are no publications to date probing bioenergetics following functional activation (e.g. using visual stimulation in the primary visual cortex). If bioenergetics at baseline is distressed but compensated in SZ, what happens if we increase energy demand above baseline? Second, there is no work on the dynamic evolution of these abnormalities in at risk conditions, first episode, and chronic disease. Such evolution may be expected since glutamatergic signaling is elevated early on in SZ and is impoverished in chronic disease. Are bioenergetics processes coupled or decoupled from glutamatergic neurotransmission during this evolution? Third, antipsychotic medication effects on these measures have not been explored in detail, especially in vivo. Fourth, the relationship between brain bioenergetics and peripheral abnormalities in SZ is not known, although these processes are closely related in healthy individuals (43). This relationship is not only of academic interest: individuals with SZ have a significantly shortened life expectancy and the primary causes of death that account for this shortening are cardiovascular and cerebrovascular (44). The major risk factor for premature death in SZ is the metabolic syndrome, a condition common in the population but enriched in SZ characterized by truncal obesity, type-2 diabetes, hypertension, and lipid abnormalities (45). And one major feature of the metabolic syndrome is abnormal bioenergetic processes in the body (46).

To answer these important questions, I argue that 31P -MT-MRS technology is the appropriate tool. MR-based and positron emission tomography (PET) methods currently available have limitations such as high cost (15O/17O gas, 13C labeled glucose), are invasive or have low sensitivity (17O and 13C MRS methods) (47-54), or only indirectly reflect the molecular machinery of cerebral bioenergetics (CMRO2 or CMRglc). Work by our group and others indicates that the in vivo 31P MT MRS approach (14,25,55-64) is an exciting method which offers novel insights (65,66). The major obstacle to clinical applications of this approach is low sensitivity due to low intrinsic 31P signal and low brain ATP/PCr/Pi concentrations resulting in long scan times and poor spatial resolution.

Nonetheless, we are applying our 31P MRS technology to a series of patient studies. Our first study using 31P -MT-MRS at 4T in chronic SZ recently appeared (67): In this study, the PCr signal was reduced by 56% and 43% for HC and SZ groups, respectively. Based on these data we calculate a highly significant 22% reduction in CK kf in SZ

(p=0.003). As part of the 31P -MT-MRS experiment, we also found reduced parenchymal pH in SZ. This pattern suggests that the machinery of energy metabolism is dysfunctional but energy production at baseline may be compensated (perhaps via glycolysis which produces lactate and makes pH more acidic).

Using an identical 31P MT MRS protocol we have recently collected preliminary data from first episode psychosis patients. In these patients, we also find CK kf reductions in the prefrontal cortex (to be published subsequently in a full dataset). Interestingly, pH was normal in this first episode cohort. This pattern suggests that bioenergetic abnormalities exist in first episode SZ, but their downstream consequences (low pH) emerge later in the disorder. Compensatory mechanisms may keep pH normal even though the CK kf is already abnormal. An alternative interpretation may be that antipsychotic medication effects reduce pH, and these have not yet had a chance to be active. All of the studies described above have focused on the PFC, but we have also implemented the same protocols in the primary visual cortex. Using this experimental set up, we are carrying out pilot experiments in response to visual stimulation presented in 6 minute epochs (baseline, 12 minutes of stimulation broken into 2 epochs, and 12 minutes of recovery broken into 2 epochs). The data we have collected thus far suggest abnormalities in PCr and ATP responses to stimulation in individuals with mental illness.

In conclusion, the process of energy generation and utilization in the brain is a critical factor that underlies healthy information processing. By extension, abnormalities in this process may underlie faulty brain activity in schizophrenia. Emerging data supports this hypothesis by providing evidence for bioenergetics abnormalities in multiple nodes of the process in this condition. One exciting potential benefit of this research may be that bioenergetics is a well-understood process at a molecular level and it may be possible to develop small molecules to act as drugs that normalize abnormalities in this process. The use of creatine as a supplement in certain psychiatric conditions may be the beginning of such a new generation of treatment approaches, whether creatine itself proves to be a useful intervention or not.

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