Metabolomics: Open Access

Metabolomics of Psychotic Disorders

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Abstract

Metabolomics, the global study of metabolites, has recently emerged as a promising approach for identification of potential diagnostic and treatment response biomarkers for psychotic disorders. To date, numerous studies have utilised metabolomics to better understand psychotic disorders and findings from these studies have begun to converge. In this review, we briefly describe the metabolomics approach including the different platforms used to analyse metabolites in biological samples from patients. We also summarise promising metabolic and pharmaco-metabolic biomarkers reported in the current psychotic disorder literature, which point to the dysregulation of fatty acid metabolism and the imbalance in oxidants/antioxidants that is present at illness onset. Finally, we conclude with a commentary on the challenges and future contribution of the metabolomics approach within the larger biomarker discovery framework currently being utilised in the field of psychiatry.

Introduction

One of the earliest biomarker approaches in psychiatry [1] employed chromatography to detect a urinary metabolite [3,4-dimethoxyphenylethylamine, later identified as p-tyramine [2]] that formed a controversial “pink spot” on paper chromatographs among those with schizophrenia but not controls. Since then, genomic (i.e., global sequence variation) and transcriptomic (i.e., global gene expression) approaches have dominated biomarker discovery efforts in psychotic disorders. However, the global study of metabolites (i.e., metabolomics) has emerged as a promising approach for identification of potential diagnostic and treatment response biomarkers for psychotic disorders. Whilst metabolomic studies of psychotic disorders are in their infancy, convergence in the current evidence is already emerging. In this review we briefly describe the metabolomics approach, summarise promising metabolic and pharmaco-metabolic biomarkers reported in the current psychotic disorder literature, and conclude with commentary on the challenges and future contribution of the metabolomics approach within the larger biomarker discovery frame work currently being utilised in the field of psychiatry.

The Metabolomics Approach

Detailed descriptions of protocols and platforms used in metabolomic studies have been presented elsewhere [3-5]. Metabolites can be separated from a variety of tissue types and quantified using several platforms. Studies of psychotic disorders have utilised Cerebrospinal Fluid (CSF), plasma/serum, erythrocytes, urine, or post-mortem brain tissue to identify metabolic signatures that differentiate patients from controls. Post-mortem brain and CSF samples are naturally preferred in the study of psychotic disorders but in practice, tissue that is more clinically accessible such as plasma or urine is typically used. The most common platforms used to interrogate the metabolome include Gas Chromatography with Mass Spectroscopy (GC-MS), Liquid Chromatography with Mass Spectroscopy (LC-MS), Liquid Chromatography Electrochemical Array detection (LCECA), and Nuclear Magnetic Resonance spectroscopy (NMRS). Platform selection is highly dependent on the experimental aims of the study. Importantly, none of the metabolomic platforms are capable of characterising all metabolites present in a particular biological sample [6]. In addition, each platform has drawbacks regarding sample processing, time and equipment required, resolution, and robustness. Thus, it has been advocated that a combination of platforms should be used on each sample to provide the most comprehensive metabolic information [4,7].

Metabolomics of Psychotic Disorders

Metabolic markers of psychotic disorders

Metabolomic studies to date have identified several metabolic abnormalities in patients with psychotic disorders compared to controls (Table 1). The most consistently reported metabolic perturbations are in pathways common to fatty acids and the pro-oxidant/antioxidant balance. Two large studies involving first episode drug naïve patients with schizophrenia showed significant increases in serum fatty acids [8] and the Cerebrospinal Fluid (CSF) metabolic profile(including increased glucose and decreased acetate and lactate) [9]. These changes were at least partially ameliorated with antipsychotic treatment; where treatment with atypical antipsychotics for nine days normalised the CSF metabolic profile of 50% of patients with schizophrenia [9] but not with typical antipsychotics (e.g. fluphenazine, haloperidol or perazine). The authors noted that when compared to patients with acute paranoid schizophrenia, patients who had received antipsychotics during their first psychotic episode were more likely to have a normalisation in metabolic profile than those who did not. Conversely, nine days of treatment with typical antipsychotics normalised fatty acids whilst atypical antipsychotics had no significant effect [8]. A third large study involving patients with schizophrenia who were either first episode antipsychotic naïve or had relapse and been medication free for at least one month, measured metabolites in both serum and urine [10]. The

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| Pathway                               | Metabolite             | Platform | Tissue | Sample Size | Concentration relative to controls | Reference |
|---------------------------------------|------------------------|----------|--------|-------------|-------------------------------------|-----------|
| **Fatty acid metabolism**             |                        |          |        |             |                                     |           |
| glycerate                             | GC-MS                  | serum    | 222    | 112         | ↑                                   | [15]      |
| eicosanoic acid                       | GC-MS                  | serum    | 222    | 112         | ↑                                   | [15]      |
| beta-hydroxybutyrate                  | GC-MS, NMR             | serum, urine | 222 | 112         | ↑                                   | [15]      |
| palmitic acid                         | GC-MS                  | serum    | 36     | 18          | ↓                                   | [11]      |
| linoleic acid                         | GC-MS                  | serum    | 36     | 18          | ↓                                   | [11]      |
| oleic acid                            | GC-MS                  | serum    | 36     | 18          | ↓                                   | [11]      |
| stearic acid                          | GC-MS                  | serum    | 36     | 18          | ↓                                   | [11]      |
| unsaturated fatty acids               | NMR                    | plasma   | 22     | 11          | ↑                                   | [12]      |
| **Glycerolipid metabolism**           | glycerol               | serum    | 36     | 18          | ↑                                   | [11]      |
| **Carbohydrate metabolism**           |                        |          |        |             |                                     |           |
| pyruvate                              | GC-MS                  | serum    | 222    | 112         | ↑                                   | [15]      |
| lactate                               | NMR                    | CSF, serum | 152 | 82          | ↓                                   | [14]      |
| glycerol                              | GC-MS                  | serum    | 36     | 18          | ↑                                   | [11]      |
| **Glycolysis**                        | glucose                | GC-MS    | serum  | 36          | 18                                  |           |
|                                      | NMR                    | CSF, serum | 152 | 82          | ↑                                   | [14]      |
|                                      | NMR                    | urine    | 22     | 11          | ↑                                   | [12]      |
|                                      | NMR                    | plasma   | 22     | 11          | ↑                                   | [12]      |
| **Amino-acid metabolism**             |                        |          |        |             |                                     |           |
| cystine                               | GC-MS                  | serum    | 222    | 112         | ↓                                   | [15]      |
| ornithine                             | FIA-MS                 | plasma   | 481    | 213         | ↑                                   | [21]      |
| arginine                              | FIA-MS                 | plasma   | 481    | 213         | ↑                                   | [21]      |
| glutamine                             | FIA-MS                 | plasma   | 481    | 213         | ↑                                   | [21]      |
| histadine                             | FIA-MS                 | plasma   | 481    | 213         | ↑                                   | [21]      |
| 1,3-Bisphosphoglycerate               | GC-MS                  | serum    | 36     | 18          | ↓                                   | [11]      |
| valine                                | NMR                    | urine    | 22     | 11          | ↑                                   | [12]      |
| trimethylamine-N-oxide                | NMR                    | urine    | 22     | 11          | ↑                                   | [12]      |
| **Inositol phosphate metabolism**     |                        |          |        |             |                                     |           |
| myo-inositol                          | GC-MS                  | serum    | 36     | 18          | ↑                                   | [11]      |
| glucuronic acid                       | GC-MS                  | serum    | 36     | 18          | ↑                                   | [11]      |
| **Alanine, aspartate and glutamate metabolism** | |          |        |             |                                     |           |
| alanine                               | NMR                    | plasma   | 22     | 11          | ↑                                   | [12]      |
| N-acetylaspartate                     | GC-MS                  | serum    | 36     | 18          | ↓                                   | [11]      |
| aspartate                             | GC-MS                  | serum    | 36     | 18          | ↓                                   | [11]      |
| **Glycine, serine and threonine metabolism** | glycine                 | GC-MS    | serum  | 36          | 18                                  |           |
|                                      | NMR                    | plasma   | 22     | 11          | ↑                                   | [12]      |
|                                      | NMR                    | urine    | 22     | 11          | ↑                                   | [12]      |
| **Tricarboxylic acid cycle**          | citrate                | GC-MS    | serum  | 36          | 18                                  |           |
|                                      | NMR                    | urine    | 22     | 11          | ↑                                   | [12]      |
|                                      | α-Ketoglutarate        | GC-MS    | serum  | 36          | 18                                  |           |
|                                      | NMR                    | urine    | 22     | 11          | ↑                                   | [12]      |
| **Vitamin E metabolism**              | γ-Tocopherol           | GC-MS    | serum  | 36          | 18                                  |           |
| **Uric acid metabolism**              | allantoin              | GC-MS    | serum  | 36          | 18                                  |           |
| **Purine metabolism**                 | uric acid              | UPLC-MS/MS | plasma | 22          | 11                                  |           |
| **Tryptophan metabolism**             | tryptophan             | GC-MS    | serum  | 36          | 18                                  |           |
| **Fatty acid amides**                 |                        |          |        |             |                                     |           |
| Metabolite                  | Method          | Measurement | Mean (SD) | p-value |
|----------------------------|-----------------|-------------|-----------|---------|
| oleamide                   | LC-TOF-MS       | serum       | 129 70 59 |         |
| linoleamide                | LC-TOF-MS       | serum       | 129 70 59 |         |
| hepatodecenoic amide       | LC-TOF-MS       | serum       | 129 70 59 |         |
| palmitic amide             | LC-TOF-MS       | serum       | 129 70 59 |         |
| palmitoleic amide          | LC-TOF-MS       | serum       | 129 70 59 |         |
| myristic amide             | LC-TOF-MS       | serum       | 129 70 59 |         |

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**Antioxidants**

| Metabolite                  | Method          | Measurement | Mean (SD) | p-value |
|----------------------------|-----------------|-------------|-----------|---------|
| total antioxidant status    | spectrophotometric assays | plasma       | 197 49 102 |         |
| glutathione                | spectrophotometric assays | erythrocytes | 197 49 102 |         |
| glutathione peroxidase      | spectrophotometric assays | erythrocytes | 197 49 102 |         |
| catalase                   | spectrophotometry | erythrocytes | 68 23 45  |         |
| taurine                    | NMR             | urine       | 22 11 11  |         |

**Oxidants**

| Metabolite                  | Method          | Measurement | Mean (SD) | p-value |
|----------------------------|-----------------|-------------|-----------|---------|
| homocysteine               | HPLC            | plasma      | 38 19 19  |         |
| protein carbonyl content   | ELISA           | plasma      | 38 19 19  |         |
| 3-Nitrotyrosine            | ELISA           | plasma      | 38 19 19  |         |
| thiobarbituric acid reactive substances | spectrophotometry | plasma      | 38 19 19  |         |
| xanthine oxidase           | spectrophotometry | cytosol of occipital cortex | 24 12 12  |         |
| phospholipids              | FIA-MS          | plasma      | 481 265 216 |         |
| lysophosphatidylcholine     | UPLC-MS/MS      | plasma      | 22 11 11  |         |
| phosphatidylcholine        | UPLC-MS/MS      | plasma      | 22 11 11  |         |
| Cytokines                  | ELISA           | serum       | 118 61 57 |         |
| Steroid biosynthesis       | ELISA           | serum       | 118 61 57 |         |
| cholesterol                | GC-MS           | serum       | 36 18 18  |         |

**Lipoproteins**

| Metabolite                  | Method          | Measurement | Mean (SD) | p-value |
|----------------------------|-----------------|-------------|-----------|---------|
| low-density lipoprotein     | NMR             | plasma      | 22 11 11  |         |
| very low-density lipoprotein| NMR             | plasma      | 22 11 11  |         |
| high density lipid protein  | NMR             | plasma      | 22 11 11  |         |
| lipid                      | NMR             | plasma      | 22 11 11  |         |
| lipoprotein                 | NMR             | plasma      | 22 11 11  |         |

**Other pathways**

| Metabolite                  | Method          | Measurement | Mean (SD) | p-value |
|----------------------------|-----------------|-------------|-----------|---------|
| lactobionic acid            | GC-MS           | serum       | 36 18 18  |         |
| erythrose                   | GC-MS           | serum       | 36 18 18  |         |
| 3-indolebutyrate fragments  | UPLC-MS/MS      | plasma      | 22 11 11  |         |
| hippurate                   | UPLC-MS/MS      | urine       | 22 11 11  |         |
| creatine                    | NMR             | urine       | 22 11 11  |         |
| creatinine                  | NMR             | urine       | 22 11 11  |         |
| pregnanediol                | UPLC-MS/MS      | urine       | 22 11 11  |         |
| 3-hydroxybutyrate           | NMR             | plasma      | 22 11 11  |         |
| acetoacetate                | NMR             | plasma      | 22 11 11  |         |

*did not survive Bonferroni correction. CSF: cerebrospinal fluid, ELISA; enzyme-linked Immunosorbent assay, FIA-MS; Flow Injection AnalysisThermospray Mass Spectrometry, GC-MS; gas chromatography-mass spectrometry, HPLC; high performance liquid chromatography, LC-TOF-MS; liquid chromatography-time of flight-mass spectrometry, NMR; nuclear magnetic resonance spectroscopy, SZ; schizophrenia, UPLC-MS/MS; ultra-performance liquid chromatography–tandem mass spectrometry

**Table 1:** Metabolic abnormalities in patients with psychotic disorders.
metabolites that were significantly dysregulated included those in fatty acid metabolism pathways for both serum and urine, supporting the results from previous studies and demonstrating that antipsychotics are unlikely to be wholly responsible for changes in fatty acids. The amelioration of metabolic changes with antipsychotic treatment is not limited to first episode patients and may be linked with the therapeutic response, where hospitalised patients with an established diagnosis of schizophrenia who responded to risperidone treatment showed a significant improvement in the ratio of unsaturated to saturated fatty acids compared to those who did not respond [11]. What is not clear from these studies is whether the amelioration of changes to fatty acids corresponds with the therapeutic response for all antipsychotics. More comprehensive studies are needed to determine whether there is ongoing dysregulation of fatty acids in patients who did not respond to treatment, as this would show clear delineation of treatment response and may be useful as a biomarker of prognosis.

Pharmacometabolomic markers

The consistent finding of a dysregulation in the metabolic profile of individuals with psychotic disorders suggests metabolism plays an important role in psychosis. However, many of these findings have been called into question in light of the metabolic syndrome associated with the administration of antipsychotic medications (in particular with atypical antipsychotics). It is therefore pertinent to address whether there is evidence to support the idea that antipsychotic medications are responsible for the changes seen in the metabolome. Table 2 summarises recent studies that have examined the effect of antipsychotic medications on metabolic markers.

The systematic assessment of plasma and urine in first episode antipsychotic-naïve patients showed that at baseline, patient’s metabolic profiles were altered, with 32 metabolites changed compared to controls. However, after correcting for multiple testing only decreased urinary hippurate and increased plasma lysophosphatidyl choline were significantly different to controls [12]. Compared to baseline, after six weeks treatment with risperidone 28 metabolites had changed but these did not survive correction for multiple testing [12]. These results suggest that a larger cohort and more focussed panel of metabolites should be investigated in future studies.

A study including patients with schizophrenia, schizoaffective disorder or schizophreniform disorder who had been non-compliant with treatment for three weeks prior to admission, investigated the effect of antipsychotics on seven lipid classes [13]. Patients were treated with risperidone, olanzapine or aripiprazole for between two to three weeks of antipsychotics on metabolic markers. After treatment with olanzapine there were significant changes in PE, Phosphatidylcholine (PC) and Triacylglycerol (TG) and a decrease in free Fatty acids (FA) compared to baseline. Risperidone treatment increased PE, PC and Lyso phosphatidylcholine (LY) compared to baseline, whilst aripiprazole treatment only increased PE compared to baseline. Three metabolites from the PE lipid class and one metabolite from the diacylglycerol and LY classes significantly correlated with early clinical response to treatment as measured by changes in the CGI [13]. A similar albeit smaller study in unmedicated Han Chinese patients with schizophrenia, investigated the effect of risperidone on metabolic pathways in order to identify potential biomarkers of schizophrenia and of treatment response [11]. Serum was collected and the Positive and Negative Symptom Scale (PANSS) was administered at baseline and after eight weeks of risperidone treatment. There were 22 metabolites that classified patients with schizophrenia distinctly from controls. Of these, there were four from the fatty acid metabolism pathway, three from the glycolysis pathway, two from the tricarboxylic acid cycle, two from the alanine, aspartate and glutamate metabolism pathways and two from inositol phosphate metabolism [11].

In addition, patients were separated into responders and non-responders after eight weeks. In patients who responded to treatment 13 metabolites were differentially affected compared to eight metabolites in the non-responders. Of these the pathways affected included: glycolysis, purine metabolism, vitamin E metabolism, alanine, aspartate and glutamate metabolism, tryptophan metabolism, fatty acid metabolism, steroid biosynthesis, tyrosine metabolism and carbohydrate metabolism. Four of the metabolites (from the glycolysis, steroid biosynthesis and carbohydrate metabolism pathways) were commonly affected between the responders and non-responders, indicating that the changes in these four metabolites are probably due to a drug effect [11]. Overall, these data confirm a dysregulation in fatty acids in schizophrenia and suggest that antipsychotics may partially correct disturbances in metabolites in schizophrenia and that changes in metabolites are associated with an improvement in symptoms. However, it is currently unclear why there is a disturbance in fatty acids in schizophrenia.

Hypotheses related to current metabolomics findings

There are several hypotheses for the dysregulation of fatty acids and/or the pro-oxidant/antioxidant imbalance commonly reported in schizophrenia. One hypothesis postulates that there may be interplay between increased lipid peroxidation resulting from oxidative stress and lack of antioxidants, which may account for the dysregulation of fatty acid pathways. Some studies have reported an elevation of lipid peroxidation in patients with schizophrenia and this has been attributed to an elevation in homocysteine [14,15].

The first study [14] investigated lipid peroxidation as measured by Thiobarbituric Acid Reactive Substances (TBARS), as well as 3-nitrotirosine-containing proteins (3-NCP), homocysteine and protein carbonyl content (PCC; a measure of oxidative damage to proteins) in patients with schizophrenia. All measures were significantly elevated in patients compared to controls, and there was a strong positive correlation between levels of homocysteine and TBARS, 3-NCP and PCC in schizophrenia. Given that oxidation is thought to increase with age and therefore be a potential confound in studies of factors investigating oxidative stress, it is important to note that patients in this study were less than 40 years of age. In the second study [15], markers of oxidative stress were measured among patients in the early (<10 years since illness onset) and late (≥ 10 years since illness onset) stages of schizophrenia and compared to controls. They showed that interleukin-6, TBARS and PCC were significantly higher in both patient groups compared to controls. In addition, interleukin-10 was significantly decreased in patients in the early and late stages compared to controls, albeit only among the late stage patients was the decrease statistically significant [15].

Another hypothesis that explains the dysregulation of fatty acids in schizophrenia postulates that because the glucose demand is higher in the brains of patients with schizophrenia ketones are substituted, which are derived from fatty acid metabolism, driving an increase in fatty acid synthesis [10]. Currently, it is unclear why glucose demand...
| Pathway                              | Metabolite                          | Sample Size       | Platform | Tissue | N | SZ | Controls | Antipsychotic | Length of treatment | Concentration relative to pre-treatment | Reference |
|-------------------------------------|-------------------------------------|------------------|----------|--------|---|----|----------|---------------|-------------------|----------------------------------------|-----------|
| Lipid class                         | free fatty acids                   |                  | HPLC     | plasma | 43| 27| 16      | olanzapine    | 2-3 weeks         | ↓                         | [13]       |
|                                    | phosphatidylcholine                |                  | HPLC     | plasma | 43| 27| 16      | olanzapine    | 2-3 weeks         | ↑                         | [13]       |
|                                    | phosphatidylethanolamine           |                  | HPLC     | plasma | 43| 27| 16      | olanzapine    | 2-3 weeks         | ↑                         | [13]       |
|                                    | lysophosphatidylcholine            |                  | HPLC     | plasma | 43| 27| 16      | olanzapine    | 2-3 weeks         | ↑                         | [13]       |
|                                    | phosphatidylcholine                |                  | UPLC-MS/MS| plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
| Glycolysis                          | glucose                             |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↑                         | [11]       |
|                                    | lactate                             |                  | NMR      | urine  | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | lactate                             |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
| Purine metabolism                  | uric acid                           |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↑                         | [11]       |
|                                    | uric acid                           |                  | UPLC-MS/MS| plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | uric acid                           |                  | UPLC-MS/MS| urine  | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
| Vitamin E metabolism               | γ-Tocopherol                        |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↑                         | [11]       |
| Alanine, aspartate and glutamate   | aspartate                           |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↓                         | [11]       |
| metabolism                         | Tryptophan metabolism               |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↑                         | [11]       |
| Familiar acid metabolism           | linoleic acid                       |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↑                         | [11]       |
|                                    | oleic acid                          |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↑                         | [11]       |
|                                    | stearic acid                        |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↑                         | [11]       |
| Steroid biosynthesis               | cholesterol                         |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↑                         | [11]       |
| Tyrosine metabolism                | tyrosine                            |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↑                         | [11]       |
|                                    | phenylalanine                       |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↑                         | [11]       |
| Carbohydrate metabolism            | erythrose                           |                  | GC-MS    | serum  | 36| 18| 18      | risperidone   | 8 weeks           | ↓                         | [11]       |
| Glycine, serine and threonine      | glycine                             |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
| metabolism                         | Lipproteins                         |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | lipoprotein                         |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | low-density lipoprotein             |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | very low-density lipoprotein        |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | very low-density lipoprotein/low     |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | density lipid protein               |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | lipid                               |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | unsaturated fatty acids             |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
| Antioxidants                        | taurine                             |                  | NMR      | urine  | 22| 11| 11      | risperidone   | 6 weeks           | ↓                         | [12]       |
|                                    | Amino-acid metabolism               |                  | NMR      | urine  | 22| 11| 11      | risperidone   | 6 weeks           | ↓                         | [12]       |
| Other pathways                      | trimethylamine-N-oxide              |                  | NMR      | urine  | 22| 11| 11      | risperidone   | 6 weeks           | ↓                         | [12]       |
|                                    | 3-indolebutyrate fragments          |                  | UPLC-MS/MS| plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | creatinine                          |                  | NMR      | urine  | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | creatinine                          |                  | UPLC-MS/MS| urine  | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | pregnanediol                        |                  | NMR      | urine  | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | 3-hydroxybutyrate                    |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |
|                                    | acetoa cetate                       |                  | NMR      | plasma | 22| 11| 11      | risperidone   | 6 weeks           | ↑                         | [12]       |

*did not survive Bonferroni correction. GC-MS; gas chromatography-mass spectrometry, HPLC; high performance liquid chromatography, NMR; nuclear magnetic resonance spectroscopy, SZ; schizophrenia, UPLC-MS/MS; ultra-performance liquid chromatography−tandem mass spectrometry

Table 2: Effect of antipsychotic medications on metabolic markers.
is higher in the brains of people with schizophrenia. Thus, until we understand the underlying mechanisms, efforts to address this demand will remain out of reach.

The final hypothesis is that the oxidant/antioxidant balance is disturbed in schizophrenia and that this may lead to the grey matter loss seen in first episode patients. This hypothesis was recently investigated by measuring grey matter volume in patients with first episode psychosis at baseline and then again at two years follows up [16]. In addition, glutathione, an antioxidant, was measured in erythrocytes collected at baseline. At follow up, all patients showed a significant loss of total grey matter volume in the frontal and parietal cortices of the left hemisphere only. When analysed according to diagnosis, patients with schizophrenia showed the same pattern of grey matter loss. In patients diagnosed with ‘other psychotic disorders’ only the parietal region was significantly changed and patients with bipolar disorder showed no significant changes. Interestingly, glutathione was significantly decreased in patients with schizophrenia only compared to controls and there was a relationship between glutathione levels and left temporal grey matter volume [16]. The same group investigated the balance between markers of oxidative stress and antioxidants in patients with first episode psychosis [17]. Diagnoses were confirmed as schizophrenia spectrum disorders (SCH) (48.04%), (which includes schizophrenia, schizoaffective disorder and schizoaffective disorders); Psychotic disorders: Not Otherwise Specified (PNOS) (24.51%); Bipolar disorder with Psychosis (BIP) (17.65%); and Depressive disorder with Psychotic symptoms (DEP) (9.80%). Oxidative stress was measured by analysing erythrocyte glutathione peroxidase, catalase and superoxide dismutase activities. Plasma was analysed for lipid peroxidation using lipid hydroperoxides, total antioxidants and glutathione. Total antioxidant status was significantly decreased in all diagnostic groups except for DEP and there was a between-groups effect where SCH and BIP were lower than other groups. Compared to controls, glutathione was significantly decreased in SCH only and lipid hydroperoxides were significantly lower in BIP only. Glutathione peroxide activity was significantly increased in SCH and BIP compared to controls. There was no significant difference in the oxidative stress molecules or lipid hydroperoxides between patients taking antipsychotics and patients not taking antipsychotics. There was a positive association between global assessment of functioning and total antioxidant status. This supports the notion that the balance between oxidative stress and antioxidants is disrupted in psychotic disorders in favour of oxidants and is unlikely to be mediated by antipsychotics. The relationship between global functioning and total antioxidant status is an indication of the importance the oxidant/antioxidant balance has on the quality of life of patients. This may reflect a future therapeutic target, however, the effect of modulating the oxidant/antioxidant balance in improving patient functioning needs to be explored further.

Challenges and Future Contribution of Metabolomics

We have previously described the major challenges in the search for biomarkers to aid in diagnosis, treatment and prognosis of psychotic disorders [18,19]. Common to all biomarker discovery research are challenges associated with diagnostic heterogeneity, low cross-platform comparability, immature analytic algorithms, and difficulty in verification/replication. Challenges particularly germane to the current state of metabolomics research, albeit not exclusive, include small sample sizes, population stratification, and characterisation of confounds such as diet, exercise, and comorbid disease states (e.g. cardiovascular disease). Although it is acknowledged that the perfect biomarker discovery study is likely unattainable, techniques for reducing diagnostic and population heterogeneity, technological advancements, improved statistical methods, accelerated collaborative efforts between investigators, and integration of multiple ‘omics’ approaches will enhance our ability to discover and apply biomarkers to psychotic disorders. The specific contribution of metabolomics in this effort will likely be substantial, given increasing evidence pointing to metabolites as the final product of interactions between genotypic variation, expression, translation, molecular networks, and the cellular environment. Thus, we suspect a relatively steep incline in metabolomics research over the next decade that will most definitely aid in our ability to identify, understand, and treat psychotic disorders in the future.

Conclusion

Metabolomics whilst in its infancy has so far suggested a dysregulation of fatty acids in psychotic disorders that may be associated with an imbalance of oxidants and antioxidants. This dysregulation is present at illness onset and therefore is likely not mediated by antipsychotic medication. What is unclear is whether this dysregulation is present before illness onset and could be useful as a biomarker of those at risk of developing a psychotic episode. It is also unclear whether the changes in fatty acids have any effect on the symptoms of psychotic disorders such as schizophrenia. Albeit a recent trial [20] suggested long-chain omega-3 fatty acids may reduce positive (e.g. delusions, hallucinations) and negative (e.g. flat affect, apathy) symptoms as well as reduce the risk of progressing to psychosis among youth with sub threshold states. Although there is some evidence that antipsychotics may ameliorate the changes in fatty acids and that this may be associated with treatment response, these effects need to be investigated more thoroughly while addressing other methodological challenges previously mentioned.

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