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Review article

Short overview on metabolomic approach and redox changes in psychiatric disorders

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ABSTRACT

Schizophrenia, depression and posttraumatic stress disorder (PTSD) are severe mental disorders and complicated diagnostic entities, due to their phenotypic, biological and genetic heterogeneity, unknown etiology, and poorly understood alterations in biological pathways and biological mechanisms. Disturbed homeostasis between overproduction of oxidant species, overcoming redox regulation and a lack of cellular antioxidant defenses, resulting in free radical-mediated pathology and subsequent neurotoxicity contributes to development of depression, schizophrenia and PTSD, their heterogeneous clinical presentation and resistance to treatment. Metabolomics is a discipline that combines different strategies with the aim to extract, detect, identify and quantify all metabolites that are present in a biological sample and might provide mechanistic insights into the etiology of various psychiatric disorders. Therefore, oxidative stress research combined with metabolomics might offer a novel approach in dissecting psychiatric disorders, since these data-driven but not necessarily hypothesis-driven methods might identify new targets, molecules and pathways responsible for development of schizophrenia, depression or PTSD. Findings from the oxidative research in psychiatry together with metabolomics data might facilitate development of specific and validated prognostic, therapeutic and clinical biomarkers. These methods might reveal bio-signatures of individual patients, leading to individualized treatment approach. In reviewing findings related to oxidative stress and metabolomics in selected psychiatric disorders, we have highlighted how these novel approaches might make a unique contribution to deeper understanding of psychopathological alterations underlying schizophrenia, depression and PTSD.

1. Psychiatric disorders

Psychiatric disorders such as schizophrenia, depression and posttraumatic stress disorder (PTSD) are severe mental disorders and complicated diagnostic entities, due to their phenotypic, biological and genetic heterogeneity and complex interactions between biological, environmental and genetic factors that cause development of these disorders. These disorders have usually unknown etiology, and their classification depends on the particular characteristic symptoms or the course of illness. Since the biological mechanisms and pathways underlying risk for these disorders are still not completely identified, there are no validated, selective and specific biomarkers for these diseases. To overcome these obstacles, „omics“ approach was proposed and used. They were promising approaches, especially genomics, since genome-wide association studies (GWAS) identified multiple genetic associations with psychiatric disorders, indicating a significant effect of heritability [70]. However, due to the polygenic nature of psychiatric disorders, GWAS indicated many genetic loci but with a ”small effect”, a questionable clinical significance, and limited biological insight [76], since numerous genetic loci associated with these disorders, biological pathways and mechanisms are yet not known. Namely, some substantial loci that might be important as risk factors or contributors for psychiatric disorders were not detected due to statistical corrections and cutoffs [70]. Besides genomics, other “omics” approaches include transcriptomics, proteomics and metabolomics (Fig. 1). These important approaches offer modern state-of-the-art techniques for understanding biological systems underlying vulnerability to psychiatric disorders and their interaction with genetic and environmental factors [83]. These methods use easy available body fluids such as blood, cerebrospinal fluid (CSF) or urine with a potential clinical utility of

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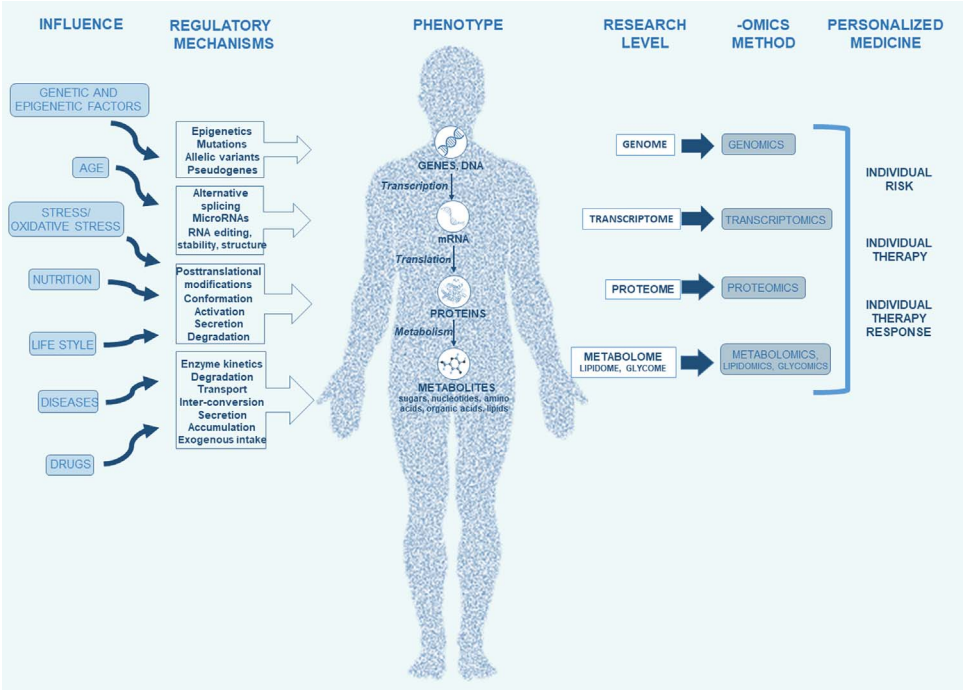

Fig. 1. Omics approach to psychiatric disorders.

selected molecules as prognostic, therapeutic and clinical biomarkers [103].

2. Metabolomics

Metabolomics is a scientific discipline dealing with small (up to 1.5 kDa) molecules called metabolites. Metabolites are endogenous low-molecular weight substances synthesized in the cells during metabolic process [26]. Metabolites, such as amino acids, lipids, nucleic acids, vitamins, carbohydrates and organic acids are the final products of the controlled cellular processes [80,101,106] that are catalyzed by various enzymes [26]. Similarly to transcriptome and proteome, the set of these endogenous biomolecules constitute the metabolome [22] that can be determined on the cellular, tissue, organ or the whole organism level [34,80]. Unlike genes and proteins, metabolites are much more diverse, and their variability depends on various genetic and environmental factors [22]. Different biological fluids or cell types have a characteristic set and concentration of metabolites [34]. Therefore, the balance between metabolites and all enzymes, cofactors, intermediates and substrates through metabolic pathways is needed to preserve homeostasis [26]. Metabolites highly reflect environmental influence, nutrition needs, effects of xenobiotics and medication, stress as well as different pathologies or internal changes in biochemical pathways of the studied system [76,82]. The metabolome includes all metabolites that are present in biological samples, such as blood, urine, cell, tissue, organ or organism, and is a result of the gene x environment interaction and/or genotype x phenotype interaction [76]. Metabolic processes reveal the activities of the gene expression and proteins, and metabolome is therefore a product of genome and proteome interacting with environmental factors, and a regulator of the metabolic homeostasis. Altered balance in some metabolic pathways leads to metabolic diseases, such as diabetes, atherosclerosis, hypertension and obesity, and causes a major health problem worldwide [26]. Due to the great importance of metabolites in biological systems, metabolite analysis as a method is increasingly used in various fields of research, since it provides improved understanding of many pathological processes through altered metabolic pathways [106].

Metabolomics offers mechanistic insights into the etiology of various diseases [103], providing comprehension of complex interactions between phenotype and genotype, and it is useful tool for understanding how cells and therefore the whole organisms function in health and diseases [83]. Therefore, metabolomics has a major impact in pharmacology, environmental sciences, toxicology, cancer, nutrition, and neuropsychiatry, for detecting potential disease biomarkers [80,106]. Biofluids used in metabolomics are CSF, plasma, urine, saliva, bronchoalveolar lavage fluid, digestive fluids, synovial fluid, cyst fluids and amniotic fluids, while platelets and CSF are the most commonly used for human metabolomic studies of psychiatric and neurological diseases [5,80,106].

There are two main approaches to metabolite analysis: i) untargeted (or non-targeted) metabolomics is the hypothesis generating, global unbiased analysis of all the small-molecule metabolites present within a biological system, under a given set of conditions [63]. It usually works by differential analysis of two or more groups in a semi-quantitative manner. This is strict sense what metabolomics means; ii) targeted metabolomics refers to studies aiming to measure specific known molecules, focusing on one or more related metabolic pathways which have been defined as biologically relevant in previous studies. Therefore, methods with high levels of specificity, precision and accuracy are applied. The potential of metabolomics lies in disease marker discovery and detection, but also in drug discovery, treatment response and in markers of toxicity. Altered metabolite levels can be detected at baseline and after treatment, with the aim to identify specific metabolites associated with good or poor therapeutic response, or development of medication side effects. The extraction, quantification, identification and interpretation of different metabolites require sophisticated analytical technologies, statistical methods for data interpretation, as well as bio-statistical and multi-variant methods [9,43,82]. Analytical techniques, including mass spectrometry (MS), coupled to different separation techniques and nuclear magnetic resonance (NMR) produce data on a large number of metabolites (Table 1), although additional technologies are required for metabolites that appear and act at lower concentrations [26]. Therefore, most data on all metabolites from a single sample are obtained from different analytical platforms. MS/chromatography and NMR are basic strategies for metabolomics [26,34,91].

While MS relies on mass to charge ratio of ionized particles, NMR spectroscopy uses magnetic properties of certain nuclei, such as ^{1}H, ^{13}C,