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Obesity and psychotic disorders: uncovering common mechanisms through metabolomics

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Primary obesity and psychotic disorders are similar with respect to the associated changes in energy balance and co-morbidities, including metabolic syndrome. Such similarities do not necessarily demonstrate causal links, but instead suggest that specific causes of and metabolic disturbances associated with obesity play a pathogenic role in the development of co-morbid disorders, potentially even before obesity develops. Metabolomics – the systematic study of metabolites, which are small molecules generated by the process of metabolism – has been important in elucidating the pathways underlying obesity-associated co-morbidities. This review covers how recent metabolomic studies have advanced biomarker discovery and the elucidation of mechanisms underlying obesity and its co-morbidities, with a specific focus on metabolic syndrome and psychotic disorders. The importance of identifying metabolic markers of disease-associated intermediate phenotypes – traits modulated but not encoded by the DNA sequence – is emphasized. Such markers would be applicable as diagnostic tools in a personalized healthcare setting and might also open up novel therapeutic avenues.

Introduction

Obesity is characterized by excess body fat, which is predominantly stored in adipose tissue. The prevalence of obesity and its associated co-morbidities – including non-alcoholic fatty liver disease (NAFLD), type 2 diabetes and cardiovascular disease – has steadily increased over the last 40-50 years, highlighting the pathogenic relevance of an obesogenic environment (Catenacci et al., 2009). Because obesity, insulin resistance, diabetes, dyslipidaemia and fatty liver tend to co-occur in the same individual, it has been useful to refer to this cluster of manifestations as 'metabolic syndrome'. The clustering of these pathologies is not considered a random event: rather, they probably have common pathogenic mechanisms. As our information technology becomes more sophisticated and patient epidemiological data are better integrated, our understanding of metabolic syndrome is becoming progressively enriched. In particular, it is now clear that there is a high prevalence of metabolic disturbances in individuals with schizophrenia and other psychotic disorders (Saarni et al., 2009; Suvisaari et al., 2007). Thus, the pathogenic mechanisms involved in metabolic syndrome might also contribute to the development and/or acceleration of these psychiatric disorders (although the converse could also be true).

Complex diseases have an undeniably strong genetic component. For example, heritability is estimated at 40% or more for metabolic syndrome (Lusis et al., 2008) and 65% or more for schizophrenia (Lichtenstein et al., 2009). Despite this, it is becoming increasingly evident that current approaches used to study genetic associations with disease traits explain only a small fraction of the known disease heritability (Maher, 2008). According to a systems biology view, most of the genetic component of complex disease susceptibility is not individual genes, but in their interactions with other genes and with the environment (Tang et al., 2009). In this context, the measurement of traits that are modulated but not encoded by the DNA sequence – commonly referred to as intermediate phenotypes (Meyer-Lindenberg and Weinberger, 2006) – is of particular interest.

Changes in the concentration of specific groups of metabolites (small molecules generated in the process of metabolism) are sensitive and specific to pathologically relevant factors such as genetic variation (Illig et al., 2010), diet (Holmes et al., 2008), development (Nikkilä et al., 2008), age (Maeba et al., 2007), immune system status (Oresic et al., 2008b) and gut microbiota (Martin et al., 2007; Velagapudi et al., 2010). Although the importance of studying metabolites in the context of health and disease was recognized decades ago (Pauling et al., 1971), analytical tools were not previously available to study metabolites comprehensively. This has changed over the past decade, with several important advances in analytical and bioinformatics technologies that enable the sensitive and comprehensive measurement of metabolites in biological systems (Goodacre et al., 2004; Katajamaa and Oresic, 2007). Thus, metabolomics – the global study of metabolites – has rapidly emerged as a powerful tool for characterizing complex phenotypes and identifying biomarkers of specific physiological responses (Oresic et al., 2006). Notably, the metabolome is sensitive to both genetic and environmental factors, which makes metabolomics a powerful phenotyping tool for personalized medicine.

This article provides a brief overview of recent advances in metabolomics as applied to biomarker discovery and the elucidation

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of mechanisms underlying obesity and its co-morbidities, with specific emphasis on metabolic syndrome and psychotic disorders.

Assessing individuals versus populations

It is thought that metabolic dysfunction can arise in part from lipotoxicity caused by lipid intake that exceeds what an individual's adipose tissue can store (Unger, 1997; Virtue and Vidal-Puig, 2010). The capacity of adipose tissue to store lipids depends on genetic and environmental factors. There is convincing evidence from epidemiological studies that there is a near-linear relationship between body weight (i.e. lipid storage) and insulin resistance. However, such an association might be due to the 'averaging effect' of a population-wide analysis. The adipose tissue expandability hypothesis suggests that, for each individual, there is a threshold for body weight that depends on the capacity of that individual's adipose tissue to store lipids (Virtue and Vidal-Puig, 2008). Exceeding this body weight threshold is accompanied by a notable decrease in insulin sensitivity due to an overload of lipids and their flux to other peripheral organs. According to this hypothesis, the increase in body weight would still linearly associate with insulin sensitivity, on average. However, the information about each individual's adipose tissue expandability threshold is lost in a population-wide analysis.

Traditionally, molecular biomarkers such as those obtained by metabolomics have been associated with specific clinical end-points in epidemiological studies. Such markers can perform statistically well in large population settings but, as explained above, might hold little value when applied to individuals. Instead, biomarkers should be sensitive to the organ-specific genetic vulnerability and to specific pathophysiological mechanisms leading to obesity-related complications. For example, a biomarker that is sensitive to the metabolic status of adipose tissue could be used to identify individuals whose adipocytes are close to reaching lipid storage capacity – and who are therefore at risk of developing insulin resistance owing to increased body weight. Finding such biomarkers would provide powerful tools for detecting persons at risk much earlier than is currently possible, and would enhance personalized healthcare.

The lipidome in health and disease

Sensitive platforms for global and quantitative studies of lipids from the cellular to organism level have been lacking. Recently, however, 'lipidomics' has emerged as a discipline closely related to metabolomics; this approach globally assesses lipidomes, comprising pathways and networks of cellular lipids in biological systems (Oresic et al., 2008a). Lipids are a diverse group of essential metabolites with many key biological functions, such as acting as structural components of cell membranes, energy storage sources and intermediates in signalling pathways. Lipids are under tight homeostatic control (Oresic et al., 2008a), and exhibit spatial and dynamic complexity at multiple levels. It is thus not surprising that altered lipid metabolism has a global reach as a pathogenic mechanism and is involved in diabetes and lipotoxicity-induced insulin resistance (Medina-Gomez et al., 2007; Medina-Gomez et al., 2009; Unger, 1997), Alzheimer's disease (Han et al., 2001; Oresic et al., 2011a), schizophrenia (Kaddurah-Daouk et al., 2007; Oresic et al., 2012; Oresic et al., 2011b; Schwarz et al., 2008), cancer (Hilvo et al., 2011) and atherosclerosis (Lusis, 2000).

Lipidomics is considered one of the key technologies for studying metabolic disorders. For example, lipotoxicity is characterized by the overproduction of reactive (lipo)toxic lipids such as ceramides and diacylglycerols in peripheral organs. This occurs owing to increased flux of fatty acids from the adipose tissue – i.e. because an individual's capacity to store fat in their adipose tissue has been exceeded (Virtue and Vidal-Puig, 2010). When characterizing the lipid profiles of metabolic organs such as liver or muscle, it is therefore not sufficient to measure the amount of lipids in these organs; it is necessary also to consider the quality of lipids – that is, to investigate the detailed molecular composition of lipids in the tissue. Such information can be obtained by lipidomics.

Detecting early markers of metabolic disorders

Determining the metabolic profiles associated with obesity and its metabolic co-morbidities is an active area of research. For example, a large-scale metabolomics study of the Relationship Between Insulin Sensitivity and Cardiovascular Disease (RISC) cohort identified α-hydroxybutyrate as an early marker of insulin resistance (Gall et al., 2010). Several other studies also linked increased concentrations of branched-chain amino acids in the circulation with insulin resistance and risk of diabetes mellitus (Newgard et al., 2009; Pietiläinen et al., 2008; Wang et al., 2011). Lipidomic studies have also revealed that triglycerides with lower carbon number and double-bond content are associated with insulin resistance (Kotronen et al., 2009b), high liver fat (Kotronen et al., 2009a; Westerbacka et al., 2010) and diabetes risk (Rhee et al., 2011).

Because monozygotic twins share the same DNA and upbringing, the contribution of genetic and early environmental factors to adult body mass and related phenotypes is accounted for in metabolic studies involving twins. Recently, we applied mass-spectrometry-based lipidomics to study fat tissue biopsies of several sets of monozygotic twins (Pietiläinen et al., 2011). The twin pairs were discordant for body weight – i.e. in each twin pair, one was obese but metabolically compensated (i.e. 'healthy obese') and the other was of normal weight. Unexpectedly, the obese twins had higher amounts of membrane lipids containing polyunsaturated fatty acids in adipose tissues than did non-obese twins, despite having lower amounts of polyunsaturated fatty acids in their diets. To investigate whether the observed differential membrane lipid composition affected the physical properties of membranes, such as fluidity and thickness, we used comprehensive molecular dynamics simulations to model lipidomics data. This analysis indicated that the lipids in the membranes of the obese twins balanced each other such that overall membrane fluidity was unaffected. Thus, membrane lipid remodelling in obese individuals might be an adaptation that serves to maintain membrane function in expanding cells (Fig. 1). A network analysis on combined genomic, clinical and lipidomic data identified *ELOVL6*, encoding a fatty acid elongase, as a network hub involved in fatty acid remodelling in the lipid membranes from obese twins. Follow-up studies in an adipocyte cell line showed that silencing of *ELOVL6* expression prevented the maintenance of adaptive membrane lipids that was observed in obese twins. Lipidomic analyses of another cohort of morbidly obese individuals showed that this adaptation mechanism breaks down in the morbidly obese (Pietiläinen et al., 2011).

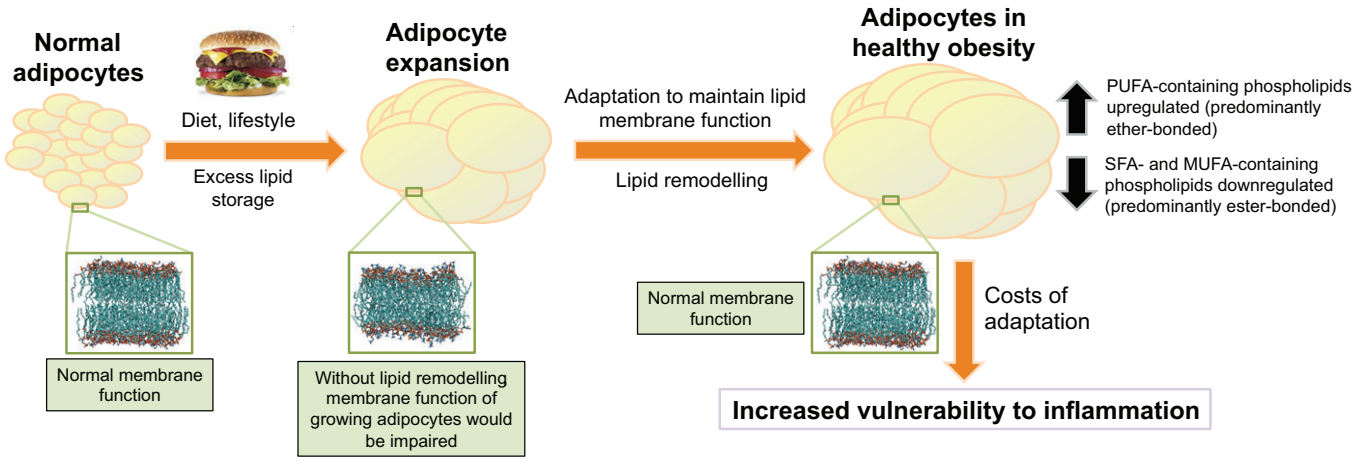

Fig. 1. A model for physiological regulation of lipid membrane composition in obesity. In healthy obesity, lipid membranes adapt as adipocytes expand in size. Given that adaptation seems to involve a relative increase in precursors of pro-inflammatory mediators, adaptation might increase vulnerability to inflammation. MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid. Reproduced with permission (Pietiläinen et al., 2011).

Notably, the types of lipids that accumulated in the membranes of adipocytes in the obese twins are precursors of pro-inflammatory lipid mediators such as leukotrienes and prostaglandins (Murphy, 2001). Thus, although membrane lipid remodelling in metabolically compensated obese individuals might help to maintain normal membrane function, it might also make the adipose tissue more vulnerable to inflammation. These findings might explain why obese individuals are at higher risk of developing inflammatory disorders such as diabetes mellitus.

The results from this twin study suggest that membranes of adipocytes hold clues about the early pathophysiological processes of obesity-associated co-morbidities. Measurement of adipose tissue membrane lipids, or their correlates in blood, as an intermediate phenotype could therefore provide powerful early markers. The study also suggests that new opportunities might arise for the prevention or treatment of obesity-related metabolic complications if it were possible to modulate the adipose tissue lipid network to regulate membrane functional maintenance and/or the vulnerability to inflammation.

The liver is another key metabolic organ that is known to be associated with diabetes risk. NAFLD, leading to chronic liver disease and liver failure, is characterized by deposits of fat in the liver, mainly in the form of triglycerides. The prevalence of NAFLD in adults in the United States doubled from 5.51% to 11.01% between 1988 and 2008, and could reach epidemic proportions if the current rates of obesity and diabetes continue to escalate (Younossi et al., 2011). Furthermore, liver fat is a major determinant of metabolic syndrome (Cohen et al., 2011; Kotronen and Yki-Järvinen, 2008; Van Gaal et al., 2006).

Liver fat is usually determined by histology or estimated by magnetic resonance spectroscopy. The former method is highly invasive, requiring a liver biopsy, so is only applied in chronic liver conditions, whereas the latter method is too expensive for healthcare screening purposes. A non-invasive test that could be widely applied in a healthcare setting is not available, so there is an urgent need to identify molecular markers that are present in the blood that reflect the amount of fat in the liver with high sensitivity. Encouragingly, preliminary lipidomic and metabolomic studies have already provided hope that reliable biomarkers associated with NAFLD might soon be uncovered (Barr et al., 2010; Puri et al., 2007).

Assessing obesity co-morbidities beyond metabolic syndrome

Epidemiological studies have shown that obesity is associated with a higher risk of developing many diseases other than diabetes, including several cancers (Møller et al., 1994), Alzheimer's disease (Kivipelto et al., 2005) and certain psychotic disorders (Saarni et al., 2009; Suvisaari et al., 2007). These associations do not imply direct causal links between diseases, but instead suggest that the causes of and metabolic disturbances associated with obesity might also play a pathogenic role in the development of co-morbidities, potentially before obesity develops. Identification of the key metabolic disturbances might help to predict disease and point to novel preventive or therapeutic avenues. For example, in a recent study of lipidomic profiles in breast cancer tissue, we identified specific phospholipids related to cellular fatty acid synthesis (Hilvo et al., 2011); these results highlighted the same pathways that were differentially affected in obese twins (Pietiläinen et al., 2011). In individuals with breast cancer, these phospholipids were associated with cancer progression and patient survival. Our follow-up studies in cancer cell lines, which included silencing of multiple genes involved in the regulation of phospholipid metabolism, identified multiple genes behind the lipid changes observed in human tumours (Hilvo et al., 2011). The findings of this study confirm the diagnostic potential of phospholipids and demonstrate that modulation of phospholipid metabolism might lead to new therapeutic opportunities in breast cancer treatment.

The association between obesity and psychotic disorders is another domain of increasing research interest (Kaidanovich-Beilin et al., 2012). Psychotic disorders are mental disorders characterized by impaired reality testing or reality distortion.

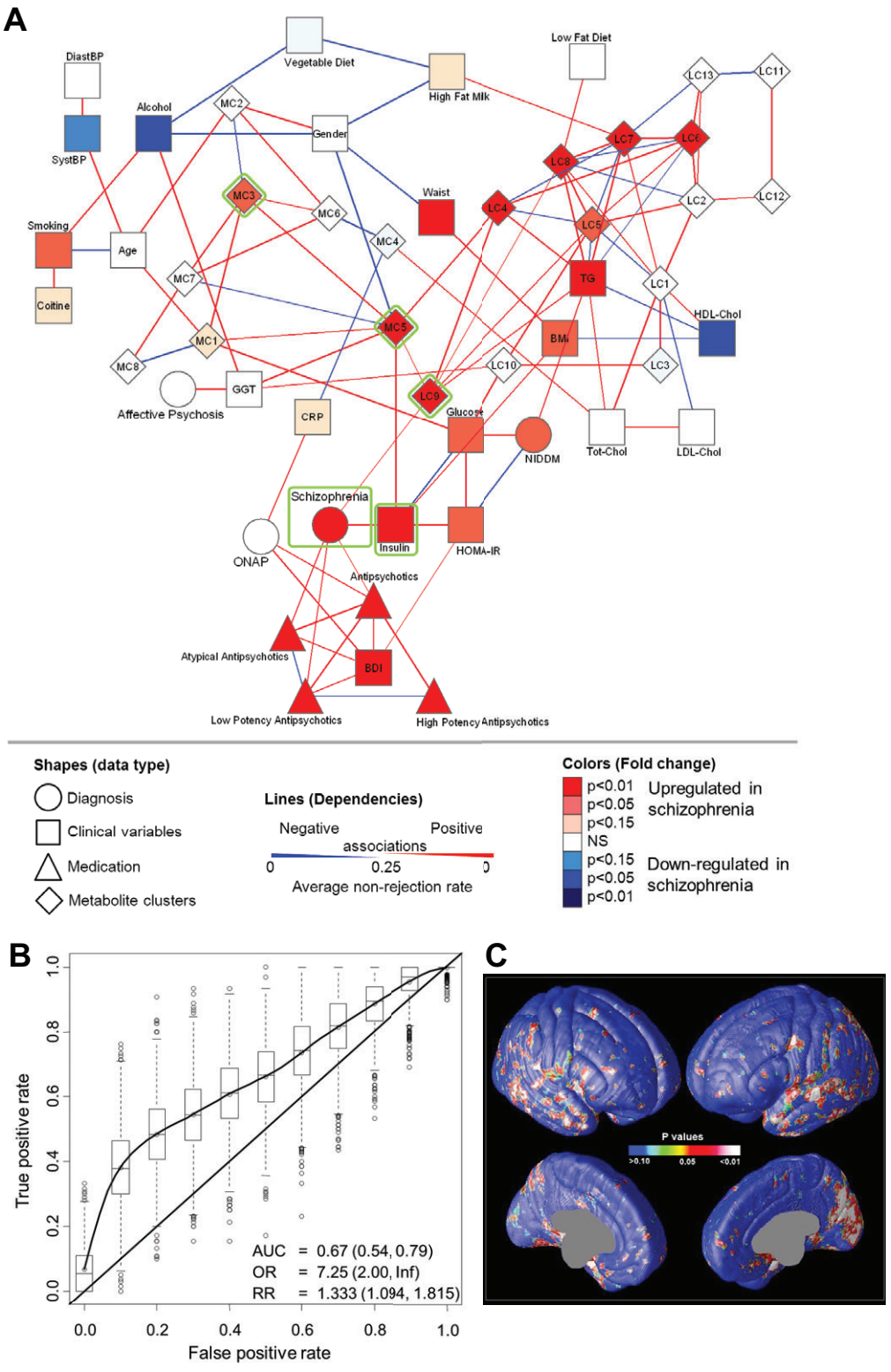

Fig. 2. Results of using systems approaches to study metabolic aspects of psychotic disorders. (A) Dependency network in schizophrenia and other psychotic disorders, in the context of other environmental, metabolic and drug-use data (Oresic et al., 2011b). Node shapes represent different types of variables and platforms, node colour corresponds to significance and direction of regulation (schizophrenia vs controls), and line width is proportional to strength of dependency. The two metabolic variables that are directly linked with schizophrenia (insulin and LC9), and two other metabolic network hubs (MC5 and MC3), are highlighted with green outlines. BDI, Beck Depression Inventory (Beck et al., 1961); BMI, body mass index; Chol, cholesterol; CRP, C-reactive protein; DiastBP, diastolic blood pressure; GGT, γ-glutamyltransferase; HOMA-IR, homeostatic model assessment index; LC, lipid cluster; MC, metabolite cluster; NIDDM, non-insulin-dependent diabetes mellitus; ONAP, other nonaffective psychosis; SystBP, systolic blood pressure; TG, total triglycerides; Tot, total. Reproduced with permission (Oresic et al., 2011b). (B) Receiver operating characteristic (ROC) curve for a diagnostic model of schizophrenia. ROC curve is a plot of the true-positive rate (sensitivity) against the false-positive rate (1 – specificity) for the different possible cut-points of a diagnostic test. A random estimate would give a point along a diagonal line (shown as a reference). The diagnostic model shown uses only concentrations of proline and triglyceride TG(18:1/18:0/18:1) to discriminate between schizophrenia and other psychoses (Oresic et al., 2011b). The key model performance parameters and their 90% confidence intervals are also shown: AUC, area under the ROC curve; OR, odds ratio (Inf, infinity); RR, relative risk. Reproduced with permission (Oresic et al., 2011b). (C) Associations between cortical grey matter distribution (four images show four different sections of the brain) and serum triglyceride levels, based on integrative analysis of MRI and plasma lipidomics in all twins participating in the study (Oresic et al., 2012). Brain regions in which cortical grey matter density is significantly negatively correlated with serum triglyceride levels are shown in red or white (see key). Reproduced with permission (Oresic et al., 2012).

Psychotic symptoms include delusions, hallucinations, disorganized speech, and bizarre or catatonic behaviour. The incidence of psychotic disorders peaks in young adulthood (Suvisaari et al., 1999), a period of development when significant changes in fatty acid composition occur in the cerebral cortex due to axonal myelination. Lifetime prevalence of these disorders is 3.5%, and the most common is schizophrenia, which has a lifetime prevalence of ~1% (Perälä et al., 2007).

It has been suggested that unhealthy lifestyle and pharmacological side effects are the main causes of excess morbidity

and mortality in individuals with psychotic disorders. Among these individuals, those with negative symptoms (i.e. with deficits in normal emotional responses or other thought processes) are more prone to being overweight and to developing metabolic syndrome. These individuals also have less healthy and more sedentary lifestyles, which might induce increased cardiovascular morbidity (Arango et al., 2011). A confounding issue is that the use of antipsychotic drugs, especially second-generation drugs, has been consistently associated with weight gain, insulin resistance and development of metabolic syndrome (Correll et al., 2011). For example, after only 6 months of treatment with some second-generation antipsychotics, the percentage of previously drug-naïve, first-episode adolescent patients who are at risk of developing metabolic syndrome rises from 17% to 40% (Fraguas et al., 2008). Kaddurah-Daouk et al. examined the effects of antipsychotic medication on the serum lipidome, and found significant changes in lipid metabolism after just 2-3 weeks (Kaddurah-Daouk et al., 2007). In line with these findings, gene expression studies found that antipsychotics strongly activate genes involved in lipid homeostasis (Fernø et al., 2005). This suggests that these psychotropic drugs target central nervous system neurons that also regulate mechanisms controlling energy balance and associated metabolic alterations.

Nevertheless, other evidence suggests that metabolic disruptions occur in individuals with psychotic disorders independently of drug effects. Studies from the pre-antipsychotic era of people with schizophrenia showed that the prevalence of diabetes or glucose intolerance was higher in patients than in controls (Henneman et al., 1954). A more recent study showed that abnormal glucose tolerance, hyperinsulinaemia and accumulation of visceral fat are already exhibited during the first episode, in drug-naïve patients, prior to antipsychotic treatment and independently of obesity (Kirkpatrick et al., 2012). Furthermore, unaffected first-degree relatives of people with schizophrenia have high rates of diabetes (19-30%, compared with 1.2-6.3% in the general population) (Mukherjee et al., 1989). Recent genetic studies have detected genes that increase the risk of both schizophrenia and diabetes (Hansen et al., 2011). Interestingly, it has been recently shown that endocannabinoids – a class of endogenous lipid-derived mediators that activate cannabinoid receptors – are involved in the regulation of energy conservation via signalling through cannabinoid receptors in the forebrain (DiPatrizio and Piomelli, 2012; Jung et al., 2012); notably, this brain region is crucially involved in the development of schizophrenia (Teffer and Semendeferi, 2012). Together, these observations suggest that metabolic disturbances associated with obesity also contribute to the pathogenesis of psychotic disease, and that metabolic status should be investigated as an intermediate phenotype in psychotic disorders.

Metabolomic studies have also highlighted the significance of glucoregulatory processes (Guest et al., 2010) and lipid abnormalities (Schwarz et al., 2008) in psychotic disorders, particularly in schizophrenia. Interestingly, some of the disturbances in glucoregulatory processes in first-episode psychosis seem to improve after the initiation of antipsychotic medication (Holmes et al., 2006). Lipid abnormalities in the brain that are observed in schizophrenia include alterations in free fatty acids and phosphatidylcholine in grey and white matter, and an increase in ceramides in white matter (Schwarz et al., 2008). Our recent metabolomics investigation including individuals with schizophrenia, other nonaffective psychosis (ONAP) or affective psychosis indicated that schizophrenia is associated with elevated serum levels of specific triglycerides, hyperinsulinaemia and upregulation of the serum amino acid proline (Oresic et al., 2011b). Using a network approach, we combined metabolic profiles with other clinical and lifestyle data (Fig. 2A) to create a diagnostic model that discriminated schizophrenia from other psychoses (Fig. 2B). In addition, in a recent lipidomic study of twin pairs discordant for schizophrenia, we found that the schizophrenic twins had higher triglycerides and were more insulin resistant than the healthy twins (Oresic et al., 2012). In the same study, integrative analysis of magnetic resonance imaging (MRI) and lipidomic data revealed significant associations between decreased grey matter density and elevated triglycerides in plasma (Fig. 2C). Finally, a recent study by Yang et al. found that several fatty acids and ketone bodies were elevated in the serum and urine of individuals with schizophrenia (Yang et al., 2011). These changes were similar in first-episode and chronic patients. These studies illustrate the power of network analyses and metabolomics for dissecting complex disease-related metabolic pathways, and for identifying candidate diagnostic and prognostic markers in psychiatric research.

Conclusions

There is an urgent need to identify molecular markers that will enable early detection of the pathophysiological processes leading to the co-morbidities of obesity. Although epidemiological studies detect associations between specific disease risk factors at a population level, more focus is needed on identifying and understanding disease-associated intermediate phenotypes and their markers in individuals. Markers of relevant intermediate phenotypes would be more applicable in personalized healthcare settings than are disease-associated risk factors acquired from population-wide screening because they could detect the presence of a specific disease-related pathophysiological process occurring in an individual. Furthermore, clarifying intermediate phenotypes and their markers might lead to novel therapeutic and diagnostic strategies for obesity-associated co-morbidities, including diabetes, as well as other diseases, including cancer, Alzheimer's disease and psychiatric disorders.

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COMPETING INTERESTS

The author declares that they do not have any financial or competing interests.

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