Metabolomic connections between schizophrenia, antipsychotic drugs and metabolic syndrome: A variety of players

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Running title: Antipsychotic-induced metabolic syndrome and metabolomics in schizophrenia

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ABSTRACT

Background: Diagnosis of schizophrenia lacks of reliable medical diagnostic tests and robust biomarkers applied to clinical practice. Schizophrenic patients undergoing treatment with SGAs suffer a reduced life expectancy due to metabolic disarrangements that co-exist with their own mental illness and predispose them to develop metabolic syndrome, also exacerbated by antipsychotic treatment. Metabolomics is an emerging and potent technology able to accelerate this biomedical research. **Aim:** This review focus on a detailed vision of the molecular mechanisms involved both in schizophrenia and antipsychotic-induced metabolic syndrome, based on innovative metabolites that consistently change in nascent metabolic syndrome, drug-naïve, first episode psychosis and/or schizophrenic patients compared to healthy subjects. **Main lines:** Supported by metabolomic approaches, although not exclusively, noteworthy variations are reported mainly through serum samples of patients and controls in several scenes: 1) alterations in fatty acids, inflammatory response indicators, amino acids and biogenic amines, biometals and gut microbiota metabolites (schizophrenia); 2) alterations in metabolites involved in carbohydrate and gut microbiota metabolism, inflammation and oxidative stress (metabolic syndrome), some of them shared with the schizophrenia scene (e.g., uric acid); 3) alterations of cytokines secreted by adipose tissue, phosphatidylcholines, acylcarnitines, Sirtuin 1, orexin-A and changes in microbiota composition (antipsychotic-induced metabolic syndrome). **Conclusion:** Novel insights into the pathogenesis of schizophrenia and the metabolic side-effects associated to its antipsychotic-treatment, represent an urgent request for scientifics and clinicians. Considering the biological environment that covers mental illness is a challenge needy of cutting-edge technologies such as metabolomics to strengthen solid biomarkers and preventive, diagnostic and therapeutical solutions.

Key words: schizophrenia, metabolic syndrome, metabolomics, second-generation antipsychotics, biomarker, gut microbiota, diagnosis.

1. INTRODUCTION

Severe mental illness (SMI) shows markedly reduced life expectancy compared to general population, because of physical health comorbidities (1). The relationship between SMI and metabolic syndrome (MetS) is complex. SMI may cause a predisposition to MetS; features of MetS, such as obesity, may exacerbate SMI, and there are likely to be common risk factors that contribute to both conditions (2). In 2017, schizophrenia (SCZ) affected 20 million people worldwide (3) involving a reduced life expectancy of 15–20 years due to a high prevalence of cardiovascular disease and MetS (4). There is growing evidence that these metabolic comorbidities are already present at the onset of psychosis in patients who are not obese and are medication naïve (5). Antipsychotics form the mainstay of treatment for patients with schizophrenia, but many are associated with weight gain, lipid disturbance, and glucose dysregulation, thereby contributing to the development of metabolic syndrome (6). Recent comparisons and even rankings of different antipsychotics published on the basis of their metabolic side-effects, represent examples of the growing concern about this circumstance (6–8). According to this issue, it is well known that clozapine and olanzapine are associated with the highest metabolic impact (9).

Currently, the diagnosis of schizophrenia is still based on interview of the person and family members as there are no reliable medical diagnostic tests available (10) and there are no biomarkers either that could be regularly used in clinical practice for the diagnosis (11). In recent years, “omics” methods have been applied in the search for biomarkers of schizophrenia and other diseases. These methods include genomics, transcriptomics, proteomics and the more recent field of metabolomics (12), also referred to as metabolomics, metabolic profiling or metabolic fingerprinting, among other terms. Metabolites are often end products of complex biochemical cascades that can link the genome, transcriptome and proteome to phenotype, providing an important key tool for determine relative and absolute amounts of small molecules in wide range of sample types (13).

Together, the metabolites in a sample comprise the metabolome, but no single platform can reveal the whole metabolome (14) so, currently, subsets of metabolomics are evolving: lipidomics (which focuses on the study of lipids (15)), glycomics (which describes the complete repertoire of glycans that a cell or tissue produces (16)), metallomics (which studies on biometals that support syntheses and metabolic functions of genes and proteins (17)) , microbiomics (which analyses the metabolites involved in the gut-brain axis, the so called “gut microbiota metabolome” (18)), pharmacometabolomics (which determinates the metabolic state of an individual but also provides tools for mapping the effects of drugs on metabolism and for identifying pathways that contribute to drug-response phenotypes (19)) and even a dynamic picture of the phenotype is reached in fluxomics (which considers the set of metabolic fluxes) (20). Some of them will be cited throughout this review, to provide remarkable advances on SCZ biomarkers and metabolomic research. The ability to use metabolic profiles, “metabotypes” to subclassify patients could also potentially contribute to clinical trial design and strategy to the improved prevention of SCZ (19). The following sections go

in deep with the most recent advances on the mechanistic insights into the pathologic process of SCZ.

2. METABOLIC ALTERATIONS IN SCHIZOPHRENIA

The pathophysiology of schizophrenia is extremely complicated such that there currently is no integrative hypothesis that can explain the clinical triad of negative symptoms, positive symptoms, and cognitive dysfunction in this disorder (21). Genetic studies provide evidence that schizophrenia is familial with complex polygenic inheritance and gene-environment interactions (22). To understand the pathogenesis of schizophrenia, abundant factors and mechanisms have been considered and discussed e.g., mitochondrial dysfunction (23), low-grade inflammation (24), DNA damage (25) and oxidative stress (26,27). Additionally, disturbances in neurotransmission in several neurotransmitter systems, including dopamine, serotonin, glutamate, γ-aminobutyric acid (GABA) and acetylcholine, and consequent alterations in functions of brain pathways, neural circuitry, and cellular signal transduction cascades may contribute to the pathophysiology of the disease, and are considered targets for antipsychotic (AP) drugs (22). After only six months of treatment with these substances, the percentage of previously drug naïve first episode psychosis patients at risk of developing the metabolic syndrome rises from 17% to 40% (4). This evidence suggests that these psychotropic drugs target brain regions involved in regulating energy balance and metabolism (4).

Metabolomics was initiated in combination with other "omics" technologies as an approach for identifying several significantly altered metabolic pathways, e.g. within schizophrenia post-mortem brain tissue (28). Since then, numerous studies have been published over this issue. In the last decade, high-throughput metabolomics technologies have provided additional comprehensive insights into the pathophysiological mechanisms of diseases (29). Metabolomics has recently emerged as a particularly valuable field of inquiry in psychiatry because unlike genomics, it captures the dynamic nature of the disease, and unlike proteomics, it measures the final products of complex interactions among numerous proteins, signaling cascades, and cellular environments (30). Metabolomics strategies have been divided into two distinct approaches, untargeted and targeted metabolomics, each with their own inherent advantages and disadvantages. Untargeted metabolomics is the comprehensive analysis of all the measurable analytes in a sample, including chemical unknowns, so that must be coupled to advanced chemometric techniques to reduce the extensive datasets generated into a smaller set of manageable signals (31). By contrast, targeted metabolomics provides a robust, high-throughput identification of preselected, defined groups of annotated metabolites with internal standards (32). Compared with the untargeted, targeted metabolomics has superior selective and sensitive performance while providing reproducible data (33).

2.1. Updating biomarkers research on schizophrenia

Although biomarker research has greatly advanced in recent years, no robust biomarkers of schizophrenia or psychotic disorders generally have yet been identified (29). Nevertheless, some advances deserve to be highlighted. Davison *et al.* reviewed some metabolites with significantly different levels found between schizophrenia patients and control subjects, thereby, potential metabolomic biomarkers. Some of the most consistent, include EPUFAs (essential polyunsaturated fatty acids), creatinine, and vitamin E (29).

In addition, circulating markers for systemic inflammation are cited in literature as potent indicators for schizophrenia, like C-reactive protein (CRP) (33) and albumin (34). Increased plasma CRP (35) and decreased serum albumin levels (36) have been shown in patients with schizophrenia in comparison with healthy controls. Even the CRP/albumin ratio (CAR) has been suggested to be a better indicator of an inflammatory response than CRP or albumin alone (34).

Within the progress of cell biology and synaptic physiology, lipids and amino acids were demonstrated carrying various information in the central nervous system, such as neurotransmitters, neuropeptides, and growth factors (33). On this subject, Parksepp *et al.* have reported the concentration of 21 AAs (amino acids) and 10 BAs (biogenic amines) in patients with first episode psychosis (FEP) before and after AP treatment during 5 years, showing alterations in plasma levels with taurine and alpha-AAA (alpha-aminoadipic acid) displaying the most significant changes compared to control subjects (37). Although further studies are needed for a better understanding of the impact of their circulating levels in schizophrenia, it sounds logical that AAs themselves and their derivatives BAs might have impact in psychotic disorders, considering the role of some AA and BAs as neurotransmitters and neuromodulators, among other roles (38). Otherwise, metabolomics and lipidomics studies demonstrate that in schizophrenia, the frontal cortex expresses abnormal metabolism of structural sphingolipids and NAAG (N-acetylaspartylglutamate), a neuromodulator of glutamate release (21).

Moreover, Tayeb *et al.* summarize an elevation of serum amino acids levels, specifically, glutamate, tryptophan and arginine. Glutamate is a major excitatory neurotransmitter that can also be used as an important alternative energy source in the brain when dysfunctional of glucoregulatory mechanisms occurs in schizophrenia patients (22). On the other side, tryptophan has been found to be elevated in the cerebrospinal fluid (CSF) of adult schizophrenia patients, along with one of its metabolites, kynurenic acid (KYNA), and its precursor kynurenine (22). The dysregulation of kynurenine metabolism could contribute to explain the imbalance of proinflammatory cytokines in SCZ (39). Another alteration in schizophrenia patients is the elevation in arginine levels and its downstream metabolite agmatine (22). Agmatine regulates the glutamate system, thereby its abnormal levels may trigger glutamatergic dysfunction (40). Further, another downstream metabolite of arginine is GABA. Tissue GABA levels were found to be reduced in brains of schizophrenia patients (39) pointing to aberrant glutamate release in target regions as its possible role in the pathophysiology of schizophrenia (41).

Connected to these findings, inflammatory processes both directly and indirectly interact with the central nervous system and result in neurodegeneration, microglial activation and dysfunction of hypothalamic-pituitary-adrenal (HPA) axis (34). Potential contributory elements include the high rate of generation of reactive oxygen species and the multiprotein inflammasome (22). Inflammasomes are multiprotein complexes that coordinate the activation and secretion of the pro-inflammatory cytokines IL-1β and IL-18a, which leads to neuroinflammation and neuroimmune modulation (42,43). Finally, meta-analysis findings demonstrated that uric acid levels are significantly decreased in FEP subjects but not in chronic SCZ subjects, strengthening the clinical evidence that FEP is accompanied by increased oxidative stress response based on the antioxidant role of this molecule (22,44).

2.2. Gut microbiome and biometals contribution

Meanwhile, is mandatory to highlight the bidirectional communication between brain and gastrointestinal tract, the so-called "brain–gut axis," based on a complex system that includes the vagus nerve. The enteric nervous system (ENS) produces more than 30 neurotransmitters and has more neurons than the spine (45). Hormones and peptides released by ENS into the blood circulation cross the blood-brain barrier (e.g., ghrelin) and can act synergistically with the vagus nerve, for example to regulate food intake and appetite(45). Co-metabolism between an organism and its gut microbiota generates numerous small molecules, some of them reported to be elevated in schizophrenia, such as 3-hydroxy-3-(3-hydroxyphenyl) propanoic acid (3,3-HPHPA) (46) and also indolic structure metabolites (47). Additionally, the oropharyngeal microbial composition at phylum and species levels exhibits different patterns for schizophrenia and control samples (48). Some examples are represented in the *Lactobacillus gasseri*, which appeared to be at least 400 times more abundant in schizophrenia patients compared to healthy subjects (48) or in the taxa *Veillonellaceae* and *Lachnospiraceae*, that are related to the severity of schizophrenia, according to the study of Zheng *et al.* Unfortunately, there are few studies directly assessing the impact of changes to the microbiota composition, so further research should focus on studying this key subject (49).

Finally, a special attention is required for the biometals role in SCZ. Briefly, a recent work provided the first evidence of disrupted Copper (Cu) transport by ATPase7A and ATPase7B in SCZ, resulting in a Cu-deficient state (50). Likewise, a recent meta-analysis with a total pool of 658 SCZ patients and 1008 controls, showed that serum Zinc (Zn) concentration was significantly lower in these patients (51). Although further studies are needed, metabolic functions of genes and of two/third of our proteins cannot be performed without the aid of various metal ions, so they should attract too the focus for future studies in search for potential or new biomarkers for SCZ (17).

3. NASCENT METABOLIC SYNDROME

3.1. Establishment of reference values in human metabolome

Having reference values of plasma metabolome obtained from healthy volunteers for comparing with pathological situations, can represent a valuable tool. To our knowledge, there is only one study looking exactly for that aim: the VARIETE study (52). It includes a large sample of well-characterized healthy French volunteers with a careful exclusion of subjects with medication or intercurrent disease and balanced sex ratio performed, in contrast to some similar previous studies in which recruitment was performed in the general population, lacking a complete and precise clinical and biological healthy status (53). For example, phosphatidylcholines (PCs) represent by mass more than 76% of total glycerophospholipids in those French healthy volunteers and sphingomielins (SMs) were higher in females than in males; this observation could shed light on, e.g., sexual dimorphism of the human metabolome in MetS, one of the most recent challenges of this discipline (54). In a more specific approach, Tsoukalas *et al.* established reference value ranges for targeted plasma fatty acids (FAs) in a well-defined population of healthy adults (55). Altogether, these results provide a baseline from which differences between health

and disease can be discriminated and, therefore, can contribute to early prevention and treatment.

3.2. Prevalence and risk factors of metabolic syndrome

Regarding the prevalence of MetS, available evidence indicates that in most countries 20% to 30% of the adult population can be characterized as having this disorder and it is growing in parallel with the incidence of obesity, type 2 diabetes (T2D) or insulin resistance (IR), known as multifactorial pathologies that has reached pandemic proportions (24,56,57). Criteria for MetS include central obesity, elevated blood pressure, elevated triglycerides, hyperglycemia, and low high-density lipoprotein; the presence of 3 of the 5 risk factors is consistent with a definition of MetS (58). MetS predisposes to both type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) (59).

Given the increasing prevalence of MetS worldwide, earlier identification of the disease is crucial and, consequently, the development of novel biomarkers for MetS would provide a potential tool for diagnosis and treatment (60,61). In this context, some of the more relevant findings launched by metabolomics related to the metabolic disarrangements of the MetS are collected in Figure 1 (57,62–65). Some of the data included in the figure were obtained by comparison of patient samples with nascent MetS (defined as MetS without T2DM or ASCVD) versus control subjects (62–65) and some have also been evidenced in preclinical and clinical studies to gain further mechanistic insights into the pathologic process of MetS (57).

Related to carbohydrates disruption, it is noteworthy, on the one hand, the significant increase level in nine of the ten biomarkers (squared into the dark grey line, Figure 1) and, on the other hand, the significant decrease in glutamine levels (signed by an asterisk) observed in MetS patients compared to control subjects (57). These molecules are involved in some essential roles such as 1) production of energy from different FAs and for the cell membrane structure maintenance (propionylcarnitine(66)); 2) signaling molecules keys for regulating glucose, lipid, and protein synthesis (leucine, isoleucine, valine, phenylalanine and tyrosine (66)); 3) energy balance, apoptosis and cell proliferation (glutamine (57)); 4) regulation of fat storage through balance in purine metabolism (uric acid (67)); 5) pancreatic β-cell function (glucose (57)) or 6) vital metabolic pathways like gluconeogenesis, TCA cycle or respiratory chain (lactate (57)).

Referred to gut microbiome metabolism (squared into the thin and soft grey line, Fig. 1), serum samples of MetS patients were studied; trimethylamine N-oxide (TMAO) concentration was linked to dysbiosis and was found as a strong marker of cardiovascular events as it modulates the glucose metabolism in the liver, triggering inflammation in the adipose tissue and influencing lipid absorption and cholesterol homeostasis (57,68). Also, intermediate metabolites such lactate, acetate and succinate, from the carbohydrate fermentation of some bacterial species, showed higher levels in MetS patients compared to control individuals, which was associated with alterations in relative abundance of several bacterial species: *Ruminococcus*, *Coprococcus*, and *F. prausnitzii* were reduced (derived from lactate and acetate increased levels in non-alcoholic fatty liver disease (NAFLD) patients) (57,69), the same as *Odoribacteraceae* and *Clostridaceae* (derived

from succinate increased levels in obese individuals) while *Prevotellaceae* and *Veillonellaceae* were increased (derived from succinate increased levels, too) (57,70).

About inflammation markers (squared into the thick and soft grey line, Figure 1), only lysophosphatidilcholines (LPCs), adiponectin (Adpn) and N-acetyl-D-tryptophan (NAT) levels were decreased, while the rest of markers levels were increased (57). Going slightly over each of them, lysophospholipids are molecules derived from the hydrolysis of phospholipids, which modulate processes such as insulin production, insulin sensitivity and inflammation (through interactions with G protein-coupled receptors) and are related to fatty liver, steatohepatitis, diabetes and obesity (57). Lysophosphatidilcholines (LPCs) have been identified as being decreased in the plasma of obese individuals (71). Significant reduced levels of adiponectin have been reported between MetS and controls (62). Adiponectin improves insulin sensitivity and exerts anti-angiogenic and anti-atherogenic effects (72). N-acetyl tryptophan (NAT), with anti-inflammatory and antioxidant properties, was found decreased in MetS patients compared to control subjects (63). Glycosylation is one of the most common post-translational modification of secreted proteins and their misregulation is related with inflammation and multiple diseases (57) and, indeed, increased serum glycoproteins (N-acetylglycoproteins or NAG) levels are positively correlated with CRP levels (73). Therefore, an altered glycosylation pattern or "glycome" might reflect alterations in key intercellular and intracellular functions, such as protein quality control, cell adhesion, cell-cell recognition, signal transduction, cell proliferation, and cell differentiation (74). Specifically, it has also been shown that the hexosamine biosynthesis and N-acetylglucosamine pathways contribute to glucose homeostasis through N-glycan branching on the glucagon receptor (75). Inflammatory markers like interleukin (IL)-1B, IL-6, IL-8, and expression of toll like receptors (TLR-4), have been shown to be significantly increased in subjects with MetS compared to control groups (57): i) adipocytes release IL-6 and other inflammatory cytokines into circulation in patients with metabolic syndrome, and they stimulate plasma CRP production in the liver and induce insulin resistance (76); ii) TLR4 is a receptor that play a vital role in the activation of proinflammatory pathways through increased NF-kB activity (65). GABA regulates cytokines secretion from human CD4 T-Cells and its level was increased in human MetS, showing a pro-inflammatory effect (63). About D-pyroglutamic acid (PGA), although few studies have been performed, it showed a significant increase in the urine of MetS patients when compared to controls, which appeared to be pro-inflammatory (63). Finally, adipose tissue dysfunction has been shown to be involved in the proinflammatory state of MetS as evidenced by an increase in leptin and other adipokines (62,63); leptin regulates energy balance by its interactions with receptors expressed by the arcuate nucleus of the hypothalamus (72).

Last line is for oxidative stress, that appears as a risk factor when an imbalance of homeostasis happens between oxidant and antioxidant agents (57). The major and new potential biomarkers related to this process (squared into the black line, Figure 1) require more studies to turn into robust biomarkers, but they deserve to be mentioned: 1) elevated plasma allantoin concentrations (8-fold higher) were reported in patients with diabetes, compared to healthy controls, indicating an increased oxidative stress in this metabolic condition (57,77); 2) pseudouridine, an isomer of the nucleoside uridine has been described as increased in end-stage renal disease (57,78); 3) One-carbon (1C) metabolism

(consisting on the transfer of one-carbon group) is implicated in redox defense and is associated with metabolic disease, overweight and obesity, as it has been demonstrated in participants with MetS risk factors, whose serum glycine and serine were in lower concentrations than in healthy controls, and they had greater adiposity (57,79). Lastly, urinary homoserine levels had a significant reduction in patients with nascent MetS, probably promoting inflammation by an induction of gut permeability (homoserine is not one of the 20 amino acids encoded by DNA and differs from serine by the insertion of a methyl group) (65).

4. ANTIPSYCHOTICS-INDUCED METABOLIC SYNDROME IN SCHIZOPHRENIA

MetS is more prevalent in people with schizophrenia compared to the general population, and risk factors for its development include poor nutrition, sedentary behavior, cigarette smoking, and treatment with antipsychotic medications (80). In particular, some studies estimate the prevalence of the syndrome as ranging from 14.7% to 68% in patients with schizophrenia who are under drug treatment (81). Even though metabolic dysfunction is frequently detected in schizophrenia patients as a common side effect of antipsychotic agents, its established presence in first- episode and drug-naïve patients with psychoses suggests that this adverse event may be disease-specific and not the result of drug treatment (22). Atypical component of MetS in patients with schizophrenia is central obesity as reflected by increased waist circumference, which is due to expansion of the amount of abdominal fat, consisting in two components: visceral and subcutaneous; especially visceral type obesity correlates with an unfavorable course of MetS (82).

4.1. Antipsychotic classifications

SCZ treatment is based on a combination of antipsychotic drugs and psychosocial interventions (83). Antipsychotics (APs) are divided into typical (first-generation) and atypical (second-generation) drugs, when they are classified depending on its target (84). Typical antipsychotics act as blockers of dopamine 2 (D_2) receptors. Contemporary atypical antipsychotic drugs are characterized by serotonin 2A (5-HT_{2A}) antagonistic property, comparable to or even higher than their D_2 blocking potential. Some atypical antipsychotics are also potent serotonin 1A (5-HT_{1A}; aripiprazole), serotonin 1C (5-HT_{1C}; clozapine, olanzapine, risperidone), histamine 1 (H_1; olanzapine, quetiapine) and α_1 (aripiprazole, clozapine, olanzapine, paliperidone, quetiapine) and α_2-adrenergic (clozapine, olanzapine, paliperidone, quetiapine, risperidone) receptor blockers. Future drugs with dual antipsychotic and antidepressant therapeutic potential may also target trace amine-associated receptor 1 ($TAAR_1$), as well as histamine 3 (H_3) and adenosine 2A (A_{2A}) receptors (84). Moreover, antipsychotics such as aripiprazole, cariprazine and brexpiprazole are considered the ‘third generation’ exhibit prominent direct-acting agonist properties at 5-HT_{1A} receptors (85). Indeed, 5-HT_{1A} receptors are now an important therapeutic target for selection of novel antipsychotics based on a range of observations (85).

Beyond this classical classification, a new one is being established depending on the antipsychotic-induced risk level for MetS. Thereby, three risk levels has been settled for developing MetS: high (e.g. clozapine), medium (e.g. risperidone), or low (e.g. aripiprazole) (81,86). Moreover, Pillinger *et al.* have compared and ranked 18 antipsychotics on the basis of their metabolic side-effects and have examined relationships between metabolic change and age, sex, ethnicity, baseline weight and baseline metabolic parameter level (6).

Metabolomics alterations in antipsychotics-induced metabolic syndrome

The underlying mechanism for the increased prevalence of MetS among patients under SGA treatment is not well understood (81). A number of explanations have been proposed, including drug actions on lipid and carbohydrate metabolism, the tendency to accumulate intra-abdominal adiposity and fat, alterations of the hypothalamic pituitary-adrenal axis, poor blood glucose control and mitochondrial dysfunction (81). In addition, pathways related to oxidative stress reactions, dysfunctions in the autonomic nervous system activity, altered gut microbiome, aberrant immune-inflammatory system, and altered ghrelin and leptin release, have also been implicated as important contributing processes leading to MetS with the use of SGAs (87).

It is imperative to consider alterations in ghrelin and leptin level. White adipose tissue (WAT) is an active organ secreting various hormones and bioactive peptides, sex hormones and glucocorticoids, located in two depots that are represented by visceral WAT and subcutaneous WAT (72). Adipocytes from WAT have a large unilocular lipid droplet and few mitochondria, opposite from brown adipose tissue (BAT) that contain multiple lipid droplets, mitochondria, is densely innervated by the sympathetic nervous system and has extensive vascularization involved in adaptive thermogenesis (72). Little is known about the composition of adipose tissue before the initiation of antipsychotic treatment, thereby it represents an emerging and exciting research field applied to SCZ. In particular, ghrelin is a gastrointestinal peptide hormone responsible of increasing food intake through interactions with receptors in the anterior pituitary gland and the arcuate nucleus of the hypothalamus (72,88). Leptin (involved in long-term regulation) and ghrelin (fast-acting hormone) act antagonistically within the hypothalamic circuits regulating energy metabolism (88). Leptin and ghrelin appears to play a crucial role in the energy balance (modulation of hunger and satiety) and appetite (food choice), during treatment with some atypical AP (88). Ghrelin levels are unaltered in antipsychotic-naïve or minimally medicated FEP patients (89) while treatment with olanzapine decreases ghrelin levels (90). It seems paradoxical that olanzapine, known to cause increased appetite and weight gain, reduces the level of an appetite-stimulating hormone; the exact mechanism of this fact is not clearly understood, however, it may be related to increased leptin and insulin levels in these patients (90).

In this context, it should be note the relevance of having available drug-naïve patients of schizophrenia (S-DN), so they provide an excellent opportunity to understand the progress of illness and development of MetS, as they have never received antipsychotic medication in their lifetime till the point of assessment (91). Drug-naïve patients with first-episode psychosis were shown to have elevated glucose and reduced acetate and

lactate levels in their CSF in comparison to healthy controls (22). First-episode schizophrenia patients were found to have higher levels of insulin, chromogranin A (a precursor protein found in many neuroendocrine cell types, that is proteolysed to produce smaller functional peptides involved in vasodilation response, insulin secretion, hyperinsulinemia or insulin resistant conditions (92)), pancreatic polypeptide (a hormone that decreases food intake through inhibition of ghrelin and increases energy expenditure through stimulation of the sympathetic nervous system innervating BAT (93)), prolactin, progesterone, and cortisol, as well as lower levels of growth hormone (GH; subjects with GH deficiency are insulin resistant (22,94).

It should be emphasized some metabolic alterations obtained through metabolomic approaches. Recently, Leppik *et al.* have described in fasting blood samples that FEP is accompanied by a significant decline of the levels of PCs and elevation in the level of LysoPC-a-C20:4, facing 53 drug-naïve FEP patients to 37 healthy subjects (95). In addition, after 7-month antipsychotic treatment of these FEP patients, they reported a significant increase in the levels of several PCs and two LysoPCs along with a decrease in the levels of SMs. Previously, also in fasting blood samples, Kriisa *et al.* demonstrated a rise in the level of a few acylcarnitines (ACs) and significantly higher levels of epidermal growth factor (EGF), IL-4 and IL-6 (strongest inflammatory markers) in 38 drug-naïve patients with schizophrenia compared to 37 controls (96). ACs are essential compounds for the metabolism of fatty acids and represent intermediates of mitochondrial fatty acid β-oxidation, therefore ACs levels alteration could contribute to a mitochondrial dysfunction which would explain the imbalance in redox or oxidative stress status associated to SCZ (95,96). Again, seven months of antipsychotic treatment resulted in significantly reduced levels of EGF, IL-2, VEGF, IL-6, IFN-γ, IL-4, IL-8 and IL-1α compared to premedication levels but also a statistically significant increase in body mass index (BMI); therefore, it can be suggested that inflammatory processes are activated in FEP, whereas the antipsychotic drug induced amelioration of disease symptoms is accompanied by a reduction of inflammatory markers and emerging signs of metabolic syndrome (96).

In spite of their metabolic toxicity profile, clozapine, risperidone, olanzapine, quetiapine, and aripiprazole have remain among the world-top selling pharmaceuticals over the past 10 years (97). Preclinical and clinical studies have shown that, among the SGAs, olanzapine is the drug with the strongest metabolic toxicity, due to its effects on weight gain, plasma glucose levels, and other metabolic parameters (97,98). Related to this, some of the most complete clinical studies looking for a metabolic signature of SCZ in plasma, based on different metabolomics technologies are those reported by He *et al* and by Paredes *et al*. In the first one, 265 schizophrenic patients (grouped by six different APs treatments) faced to 216 healthy individuals (10), revealed five amino acids, one acetylcarnitine and six PCs with significantly different concentrations in schizophrenic subjects compared with controls (10). Paredes *et al*. showed a unique perspective, by grouping the schizophrenia patients based on antipsychotic-induced risk level for MetS, so they founded several important mediators of MetS, like insulin, TNF-α and adiponectin, to be significantly different between the SGA risk groups (86). A more recent study, with 122 recruited adults with schizophrenia, demonstrates the potential for serum metabolites to reflect bioenergetics metabolism changes with 8-week follow up of individuals with schizophrenia, especially amino-acid metabolism and fatty-acid

metabolism (8). Specifically, acylcarnitines, LysoPC and amino acids, were significantly associated with treatment of schizophrenia. Next, some recent advances on future molecular markers of MetS induced by SGAs are resumed.

Previously it has been described how SGAs act at multiple neurotransmitter receptors. Especially 5HT2A, 5HT2C and H receptors, have been reported to have an effect on food intake via the hypothalamus (87). A clinical study composed of schizophrenia patients (n=54) treated with olanzapine or clozapine (both MetS and non-MetS groups) showed that the MetS patients exhibited markedly lower plasma levels of Sirtuin 1 (SIRT1) and higher plasma levels of IL-6 than non-MetS patients and normal controls (87). A promising role for sirtuins family is predicted, so that they trigger important effects on the regulation of lipid and glucose metabolism (SIRT1 and SIRT6 can coordinate a switch from glucose to fatty acid oxidation during the acute inflammatory response) and they also suppress inflammation in both adipocytes and macrophages, which leads to a reduction of adipose tissue inflammation (99). Also remarkable is the study that shows a significant correlation between orexin-A levels and various metabolic parameters in patients receiving long-term antipsychotic treatment (100). In this study, fasting blood samples of 159 patients with schizophrenia (grouped by four different AP treatment) were compared to 60 nonpsychiatric controls, revealing that patients taking clozapine had more unfavorable plasma lipid and glucose parameters than the patients taking less obesogenic antipsychotics. Moreover, patients taking clozapine had lower orexin-A levels than less obesogenic antipsychotics (100). Orexins are neuropeptides mainly produced by neurons located in the lateral hypothalamic area and have been suggested to integrate central and peripheral signals to regulate metabolic homeostasis, through a leading role in the thermogenesis activation related to food intake, in turn involved in body weight regulation (100,101). Thereby, higher orexin-A levels are associated with a lower risk of MetS in patients with schizophrenia (100).

Finally, it cannot be omitted the relevant role for the gut microbiome – the modifiable "second genome" consisting of trillions of diverse microbes living in the human gut – as a key modulator of host organismal aging, which may contribute to premature morbidity and mortality in schizophrenia (102). Human gut microbiota is mainly composed of bacteria, with *Firmicutes* and *Bacteroidetes* as the dominant phyla, followed by Actinobacteria, Proteobacteria and Verrucomicrobia (18). It should be noticed an ambitious study developed by Nguyen *et al.* where 48 subjects with schizophrenia (treated with atypical antipsychotics (either alone or with typical) and 48 control subjects were included, showing that *Lachnospiraceae* taxa was significantly associated with schizophrenia (102), although more investigations are needed to settle on the alteration's nature, as controversial results are reported by other authors (103–105) . Furthermore, it has been found that after 24 week of risperidone treatment, schizophrenia patients have a significant increase in body weight, in low-density lipoprotein, in fasting plasma glucose, high CRP sensitivity and demonstrated increased fecal *Bifidobacterium* spp. and *E. coli*, and decreased fecal *Clostridium coccoides* group and *Lactobacillus* spp., as compared with healthy controls (106). In this complex ecosystem, metabolites are the final downstream products of microbes, which modulate the physiology of the host (18). It has been estimated that around 40 % of metabolites in the human body are related to microbiota, which highlights their relevance to human health (18). Nevertheless, it is not yet clear whether the changes in the diversity and composition of microbiota are the cause

or consequence of the brain disorders (18), suggesting a crucial field of research for focusing the underlying mechanisms of schizophrenia.

5. CONCLUSION

SCZ is a chronic, debilitating, and etiologically complex psychiatric disorder (107) whose causes point to multiple hypothesis that claim to be clarified. Apart from the evidenced genetic inheritance of SCZ (22) and the interaction between the gut-brain axis and the HPA axis (108), a wide variety of interconnected mechanisms have been considered and discussed as contributors to the pathophysiology of the disease: DNA damage (25), oxidative stress (26), mitochondrial dysfunction (23) and inflammatory processes (109); altogether trigger alterations in neurotransmission (22), neuroimmune modulation (43) and amino acid metabolisms (27), such glutamate.

Gaining knowledge of key metabolic variations associated with SCZ can be used to improve its early detection, diagnosis, and therapeutic strategies (110). EPUFAs, creatinine, vitamin E, albumin, alpha-AAA, NAAG, GABA, uric acid, PCs, Cu and Zn levels, are significantly decreased in SCZ patients compared to healthy people, together with an increased level of CRP, taurine, glutamate, tryptophan, arginine, acylcarnitines, IL-4 and IL-6 and 3,3-HPHPA, among others (see previous sections for more detail).

MetS is a disorder which represent a clinical challenge worldwide due to increasing obesity and sedentary life habits (58). Low grade inflammation and insulin resistance are pivotal players in the pathogenesis of this syndrome (63). Preclinical and clinical studies in nascent MetS patients uncover novel biomarkers, some of them compiled in Figure 1, connected to the major risk factors involved in this pathology (57). Mechanisms of SGA-induced metabolic disturbance are likely to be multi-factorial and to involve both peripheral and central mechanisms, e.g. increased appetite stimulation (111) and intra-abdominal adiposity (112), alterations of the hypothalamic pituitary-adrenal axis (81), poor blood glucose control (81), altered gut microbiome (113) and aberrant immune-inflammatory system (87).

Metabolomics has demonstrated the potential for serum metabolites to reflect bioenergetics metabolism changes (8). Clinical studies employing this technology has revealed a considerable number of putative biomarkers whose expression level is modified depending on the SGA treatment followed by the schizophrenic patients (27,86,114). A special attention deserves hormonal regulation of appetite, as it represents a crucial but still controversial item worthy to be a novel target for prevention or treatment of obesity-related comorbidities in patients with schizophrenia (72,88). In addition, SIRT1 significantly decreases in olanzapine or clozapine treated patients compared to control subjects (99) and, also, those patients with clozapine had lower orexin-A levels than patients treated with less obesogenic antipsychotics (100). In addition, *Lachnospiraceae* taxa was significantly altered in the schizophrenia group compared to control group (102,105) and fecal *Clostridium coccoides* group and Lactobacillus spp. are decreased in risperidone treated patients as compared with healthy controls, together with a demonstrated increased fecal *Bifidobacterium* spp. and *E. coli* (106).

Finally, this work not only updates a wide panel of putative biomarkers to yield an insight into the pathogenesis of SCZ or suggests an incipient metabolomic signature of the illness. Moreover, it pursues to make clinicians conscious about a huge and complex biological reality that plays along with the development of the mental disorder of SCZ, which is starting to be untangled through the role of the altered metabolic molecules in nascent MetS, drug-naïve, FEP and schizophrenic patients when compared to healthy subjects. Reaching a clinical tool able to integrate in a "ready- to-use" format all these biomarkers, could sounds dreamy. Nevertheless, already in 2013 the collaborative European project METSY (Neuroimaging platform for characterization of metabolic comorbidities in psychotic disorders) searched for identification and evaluation of robust markers able to predict and monitor psychotic and metabolic symptoms, in an attempt to alleviate the urgent need to identify biomarkers, exploiting the advantages offered by machine learning as well as semantic modeling strategies to fuse the structural brain connectivity data (4). Still further investigations are needed with larger sample size to consolidate causal associations and contribute to narrate a comprehensive story that allow prevention and/or therapeutics for SCZ.

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