The common pathophysiology underlying the metabolic syndrome, schizophrenia and depression. A review

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Background. There is a growing interest in metabolic alterations in patients with psychiatric disorders due to their increased risk for metabolic syndrome (MetS) development. Inflammation is known to underlie the pathophysiology of schizophrenia and depression as well as MetS. Vulnerability factors for schizophrenia/depression and MetS hence appear to be shared.

Methods and Results. Based on a Web of Science search, this review examines current evidence for MetS pathophysiology involving dysregulation of adipose tissue signaling – adipokines and pro-inflammatory cytokine, both also known to be aberrant in schizophrenia/depression. Further, gender differences in the incidence and course of schizophrenia/depression were reported. The disturbances linked to the MetS are also described. Therefore, this review further maps the gender differences in the psychiatric-metabolic comorbidities.

Conclusion. There is evidence supporting a pathological predisposition to MetS in both schizophrenia and depression in both humans and animal models. This predisposition is dramatically enhanced by antipsychotic medication. Further, there are gender differences from clinical findings suggesting women with schizophrenia/depression are more vulnerable to MetS development. This has not yet been assessed in animal studies. We suggest further validation of existing schizophrenia and depression animal models for the assessment of metabolic disturbances to provide tools for developing new antipsychotics and antidepressants with "metabolically inert" profile or improving the metabolic status in schizophrenic/depressed patients.

Key words: metabolic syndrome, schizophrenia, depression, sex/gender differences, adipokines, leptin, adiponectin, resistin, AFABP

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INTRODUCTION

Psychiatric disorders are commonly associated with increased morbidity and mortality largely due to other medical conditions such as cardiovascular diseases, diabetes, respiratory and infectious diseases. There is a rapidly growing interest in the assessment of metabolic disturbances in patients diagnosed with psychiatric disorders (especially schizophrenia and depression) due to their higher risk of metabolic syndrome (MetS) than the general population. In addition, growing evidence indicates a role of inflammation in the pathophysiology of these diseases.

In the US and European populations, the prevalence of MetS in psychiatric patients ranges from 25-56% (depending on definition) and it constitutes major health and financial burdens[1-3]. It is estimated to be up to 50% higher than age-matched healthy control populations[4] with expectation to rise to 59% by 2020 (ref.[5]). Moreover, not only western populations are affected but also eastern regions report a high prevalence. More particularly, Asian populations report a mean prevalence of 20-40% (ref.[6]), South American regions with 14-30% and Australia with 20-30% (ref.[1]). Further, younger age groups also show a growing rate of MetS incidence[7]. A number of reports confirm the psychiatric populations have a substantially higher incidence of MetS than the general population, especially in the case of schizophrenia[8] and depression[9].

Obesity and MetS development are also known to differ according to gender as a result of differences in the amount and distribution of body fat and differences in adipose tissue metabolism and function between the sexes[10]. The incidence of MetS was reported to be higher in women than in men in Arabic populations[11], a finding consistent with European populations[12]. Therefore, a gender-specific approach may be more effective for the treatment and prevention of MetS development.

The need for reviewing current knowledge on the shared pathophysiology linking MetS and psychiatric disorders is supported by increasing numbers of publications on the topic of comorbid MetS and schizophrenia/depression. Web of Science search (performed in August 2014) for "metabolic syndrome" and "schizophrenia*" in publication titles currently provides 186 records, with the oldest from the year 2002 including 11 reviews. However, most papers (and reviews) focus on the side-effects of anti-

psychotics and not the pathophysiological causes according to the disorders *per se* resulting in MetS. Analogous search for depression ("depress*") returns 161 publications with the oldest from the 2003 including 5 review papers.

The aim of this review was to evaluate the available findings on the link between MetS and schizophrenia/ depression with a focus on gender differences.

METABOLIC SYNDROME AND INFLAMMATION

The epidemic spread of MetS has resulted in over 2 billion overweight and obese adults worldwide[13]. This syndrome is defined as a complex of risk factors closely related to the development of atherosclerosis and subsequent cardiovascular morbidity together with type-2 diabetes. In particular, these factors comprise mainly abdominal distribution of adipose tissue (abdominal obesity), dyslipidemia, hypertension and distortion of glycemic homeostasis[14]. The seriousness of this pathology lies in increased mortality due to cardiovascular conditions and diabetes type 2. Compared to normal populations, the incidence of myocardial infarction and stroke are 3-fold higher in MetS patients; the risk of type 2 diabetes development is 5-fold higher[15]. Individuals with MetS also often manifest pro-thrombotic and pro-inflammatory states reflected by higher blood levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-12 (IL-12), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interferon-γ (ref.[16]).

Dysregulation of adipokines as biomarkers of adipose tissue metabolism plays an essential part in all obesity-related diseases. Most relevant adipokines known to be dysregulated in MetS are leptin, adiponectin (both supporting insulin signaling functions), resistin and adipocyte fatty acid binding protein (AFABP). Also pro-inflammatory cytokines are considered adipokines such as interleukins, TNF-α and C-reactive protein (CRP), all generally suppressing insulin signaling functions.

Leptin is a peripheral signaling protein that regulates the hypothalamic satiety center and adipose reserves in the body[17,18]. It is key mediator of energy homeostasis involving regulation of appetite, lipid catabolism and inhibition neurotransmitter neuropeptide Y, a known appetite stimulator[19]. Plasma levels of leptin are generally higher in obese patients, which is considered to be a leptin-tolerant state[20,21].

Adiponectin is a protein that inhibits inflammatory reactions and protects against metabolic disease, by a wide range of mechanisms, including anti-diabetic, anti-inflammatory and anti-sclerotic[22]. It is involved in the regulation of carbohydrate and lipid metabolism, inhibiting gluconeogenesis in liver and increasing the transport and utilization of free fatty acids in the periphery. Furthermore, it significantly affects the function of insulin and plays an important role in energy homeostasis, causing a decrease in body weight without affecting food intake. However, it is believed that it also directly influences the regulation of appetite and weight control[21,23].

Resistin is a peptide hormone produced by mature adipocytes and regulates insulin sensitivity[24]. Its inhibitory effect on the differentiation of adipocytes probably underlies its role in the feedback between nutritional status and adipogenesis. Its plasma levels increase in correlation with inflammatory markers including CRP, soluble TNF-α receptor-2, IL-6 and lipoproteins in combination with phospholipase A2 under pathophysiological conditions related to inflammation[25]. Based on preclinical evidence, resistin may represent a key link between inflammation and its metabolic consequences[21,26-28].

AFABP is a newly discovered adipokine found at higher plasma levels in patients who have the MetS. Patients with higher levels of AFABP have worse prognosis and increased cardio-metabolic risk factors, reversible by atorvastatin treatment[29]. Further, TNF-α is constitutively expressed in adipose tissue and this condition leads to insulin resistance in animal models of obesity which supports the face validity of the models. Plasma levels of AFABP in humans closely correlates with degree of obesity and the development of insulin resistance and positively correlates with waist circumference, blood pressure values, and parameters of lipid metabolism, serum fasting insulin and insulin resistance index[21,30].

The growing evidence has resulted in the formulation of the inflammatory hypothesis of insulin resistance and MetS (ref.[31-33]) and MetS is also associated with other inflammatory diseases such as rheumatoid arthritis[34] showing secondary development of MetS on an inflammatory basis. The hypothesis assumes obesity is a consequence of excessive caloric intake representing a sub-clinical inflammatory process, which induces insulin resistance and following clinical and biochemical manifestations of MetS as demonstrated in numerous studies. For review see Alemany et al.[31] Moreover, the inflammation is mediated by pro-inflammatory cytokines produced by macrophages which tend to populate the growing adipose tissue in obesity at higher rates[35]. In mouse obesity models, an up-regulation of specific genes for macrophages - macrophage inflammatory protein 1α (MIP-1α), monocyte chemoattractant protein-1 (MCP-1), macrophage-1 antigen (MAC-1), macrophage surface glycoproteins F4/80 and CD68; and genes promoting inflammatory processes in white adipose tissue are found. Molecular mechanisms leading to macrophage activation in obesity/ MetS are not fully understood. However, participation of adipokines (adiponectin, leptin, complement factor C3, MCP-1, cytokines, free fatty acids) is assumed[36]. Activated macrophages release several cytokines and chemokines such as TNF-α (ref.[37]), IL-1, IL-6 and MCP-1, distorting adipocyte sensitivity to insulin, which then in turn promote further activation and infiltration of macrophages. Therefore, impaired insulin signaling in adipocytes may lead to massive lipolysis, necrosis and development of insulin resistance[33,38].

PSYCHIATRIC DISORDERS AND INFLAMMATION

There is accumulating evidence suggesting that schizophrenia is associated with increased serum levels of pro-inflammatory cytokines, namely IL-1, IL-6, TNF-α and high-sensitivity CRP, even in patients with minimal or no exposure to antipsychotics[39].

Prenatal infections are also hypothesized to have serious impact on the brain, which is supported by validation of several neurodevelopmental animal models of schizophrenia based on immune or toxic prenatal insult namely: Immune: polyIC (polyriboinosinic-polyribocytidilic acid) model[40], toxic: MAM (methylazoxymethanol acetate) model[41] or Δ9-THC (Δ9-tetrahydrocannabinol) model[42]. Together with certain genetic factors, these findings provide convincing evidence that inflammation is a major factor in the pathology of this disorder[43].

There is a well-established concept of depression strongly associated with inflammation. An abundance of both clinical and preclinical data reported increases in pro-inflammatory cytokines such as IL-1, IL-6, TNF-α and CRP in depressed patients[44-47]. Similar findings were also discovered in preclinical studies[48] including the olfactory bulbectomized rodent model of depression[49].

PSYCHIATRIC DISORDERS AND METABOLIC SYNDROME

Schizophrenia and metabolic syndrome

Obesity or MetS are common in schizophrenic patients. MetS has an incidence of 3-4% in the general population, but up to 10% in schizophrenic patients even before initiation of the treatment with antipsychotics[8] which often results in typical changes in lipid metabolism[50]. It appears that not only antipsychotic treatment but the pathophysiology of schizophrenia itself is linked to MetS development suggesting a common underlying pathway- chronic inflammatory abnormality of cytokines[43]. Therefore, vulnerability factors for development of schizophrenia, diabetes, and MetS seem to be shared and interconnected. In patients with schizophrenia the risk is further greatly increased by the use of antipsychotic medication as reviewed repeatedly elsewhere[8,51-55].

More specifically, elevated blood levels of adiponectin have been reported in schizophrenia[56] and there is a correlation between serum leptin levels and body weight[51]. In addition, leptin concentration was shown to play an important part in the negative feedback against dopamine activity connected to positive symptoms of schizophrenia[57]. Furthermore, it is well known that antipsychotic treatment induces clinically relevant weight gain and rise in fasting plasma glucose levels[58].

Despite the high clinical relevance, relatively little research has been done in preclinical models of schizophrenia, which could then contribute to targeted drug development for MetS treatment in psychotic patients. Studies conducted in animals were mostly related to the evaluation of metabolic effects in all classes of antipsychotics rather than the assessment of the relation between MetS and schizophrenic phenotype *per se*. These drugs were shown to notably disturb lipid metabolism in drug naïve Sprague-Dawley rats as well as in kainic acid treated Fisher rats used as a model of schizophrenia[59,60]. This indicates that schizophrenic-like phenotype in rodent models and antipsychotic medication does lead to increase in vulnerability to metabolic disturbances further confirming their validity and translational potential evaluating gender differences, a key importance for developing new therapeutic strategies as described in the corresponding section of this text.

DEPRESSION AND METABOLIC SYNDROME

Multiple lines of evidence confirm higher incidence of MetS in depressed patients. A 50% higher prevalence of depression has been reported in individuals with MetS in an Australian population[61] and a 4-fold increased risk for MetS in patients with lifetime major depression episode in a Lithuanian population[62]. Similar outcomes in a German population were found[63]. Also, different ethnic groups were compared with consistent finding of higher MetS prevalence in depressed African-American, Caucasian[64], and Asian women[65]. Furthermore, not only major depression but also bipolar disorder has been shown to have association with MetS (ref.[66]). However, MetS seems to be specifically linked to depression as it has been repeatedly shown that anxiety is not associated with metabolic disturbances[62,67].

There are also clinical studies showing no[68] or only partial association of MetS symptoms (lipid profile) with depression[69]. However, recently, Pan et al. published an extensive meta-analysis (the first of its kind) reporting a strong link between depressive disorders and development of MetS in both genders. The results indicate a convincing bidirectional association between depression and MetS (ref.[9]). Further support (although sporadic) for the association between MetS and depression could provide a case study of a (Caucasian) woman treated with pioglitazone and showing strong antidepressant effect[70].

Suggested mechanisms underlying both disorders include HPA axis dysregulation following the inflammatory reaction. Moreover, two subtypes of depression (melancholic and atypical depression) were identified to be associated with the inflammatory and metabolic dysregulation. This highlights the possibility that not all forms of major depression possess this association with MetS (ref.[71]). Changes in important adipokine levels in depressed patients were reported compared to a healthy population suggesting predisposition to MetS development in depressed patients. In agreement, a "leptin hypothesis of depression" was formulated as low levels of leptin have been found in association with depression in humans as well as depressive behaviors in rodents. It was suggested that both leptin insufficiency and leptin resistance may contribute depressive status[72]. These findings are translated and further supported by several animal studies[73] including pharmacological experiments where

leptin induced antidepressive-like behaviour in a forced swimming test, a commonly used test for evaluation of depressive-like phenotype in rodents[74].

Blood levels of another adipokine – adiponectin – were found to be reduced in Brazilian patients with major depression before antidepressant treatment. The authors of the study (Leo et al. 2006) conclude that the reduced availability of circulating adiponectin is likely to have an impact on mood state[75]. Similar findings were reported in an Italian population[76] and later in a US population[77]. However, contradictory findings were reported in a Korean study showing higher levels of adiponectin in depressed individuals[78]. The variability could be due to antidepressant treatment which seems to increase adiponectin levels[79]. Yet, studies reporting no difference before and after treatment have also been published[80].

Regarding resistin, a positive association between blood levels and free cortisol concentrations were found in depressed patients. Resistin levels were normalized when patients remitted after pharmacological treatment but not in non-remitters[80].

ROLE OF GENDER IN THE METABOLIC SYNDROME AND PSYCHIATRIC DISORDERS

Schizophrenia and MetS: implications of gender

Sex-specific differences in the epidemiology, onset and course of schizophrenia are repeatedly reported. More specifically, men have approximately 4-times higher tendency to develop schizophrenia and the first symptoms usually appear at a younger age[81]. On the other hand, women tend to suffer more from comorbid depression while men it is drug addiction. In addition, gender differences in response to antipsychotic treatment are reported. However, a clear explanation is yet to be provided. Influences of sex hormones, sexual dimorphism of the brain, metabolic differences and social factors were so far only proposed as partial explanations[82,83]. Gender differences in MetS comorbidity with schizophrenia were found repeatedly before and after the initiation of the antipsychotic treatment with women being approximately 3-times more prone to develop MetS (ref.[8]).

Furthermore, preclinical studies have recorded gender differences suggesting a greater vulnerability (increase in body weight and metabolic changes) in female rats, specifically, the most suitable model for antipsychotic-induced weight gain appears to be the female Sprague-Dawley rat[84]. In contrast, male rats showed no significant changes in body mass yet still exhibited metabolic disturbances such as increased visceral fat mass and hormonal changes[59]. Nevertheless, increased adiposity was reported in both genders and seems to be adequately modeled in rodents with a schizophrenic phenotype. It has not yet been established which experimental paradigms most accurately reflect weight gain and metabolic abnormalities in schizophrenia, known to be increased by antipsychotic treatment in humans[85].

Depression and MetS: implications of gender

In the case of depression, reports of gender differences are only recently emerging. A similar strength of the overall association has been reported between metabolic risk factors in men and women, but in males, several factors were associated with depressive symptoms, while in females the association was confined to waist circumference only[86]. Earlier, a stronger association of MetS with depression was found in the female US population compared to male group[87] similarly in the Israeli population[88]. However, negative findings have been published as well[89]. Furthermore, depressed women showed significantly higher leptin levels than a control group both before and after the response to antidepressant treatment, whereas no difference was found between the male patients and their controls. The improvement of depression with antidepressant treatment was shown to cause a further elevation of leptin levels, in both female and male patients. Therefore, clinical response to antidepressant treatment seems to be linked to leptin metabolism[90]. In addition, adiponectin levels were found to be dysregulated in men with depression while no differences were observed in that of women[78].

CONCLUSION

In summary, there is likely a metabolic predisposition to MetS in both schizophrenia and depression patients which is evidence of underlying pathophysiology in both humans and animal models. This predisposition is enhanced by antipsychotic medication in psychotic patients. In agreement, numerous authors in clinical fields have already suggested screening for MetS in psychiatric patients to combat increased rates of morbidity and mortality from non-psychiatric reasons in these patients with early lifestyle and pharmacotherapeutic interventions. Specifically, in schizophrenic patients, routine consultation with a diabetologist has been suggested[52].

Moreover, development of new anti-inflammatory treatments for the dual pathology of schizophrenia and MetS has been proposed[91], which also could be a useful approach alleviating the cognitive symptoms of schizophrenia[92]. This evidence concerns newly diagnosed patients as well, with chronic treatment with antipsychotics being a well-known risk factor for MetS development. Thus, a follow-up monitoring of metabolic abnormalities in patients on second generation antipsychotics is strongly recommended by the consensus of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity[93].

In depression, a closer monitoring for MetS (ref.[61,63,94]) together with development of disease-modifying therapies[95] and special regards to sex-differences[96] have been repeatedly suggested. Further, the current scientific literature has suggested the validation of existing animal models and the development of newer models to better reflect psychiatric diseases[97,98].

Furthermore, the possible gender differences in clinical findings (suggesting women with schizophrenia/de-

pression are more vulnerable to MetS development) are not yet assessed in animal studies. In the light of evidence on gender differences in MetS development in psychiatric disorders, sex differences should be taken into account in future preclinical and clinical studies. However, the lack of validated animal models for assessment of metabolic disorders comorbid in psychiatric diseases is problematic. Such validation of existing animal models of schizophrenia and depression could provide a useful tool for developing innovative pharmacotherapeutic solutions with "metabolically inert" profile or even improving the metabolic status of psychiatric patients.

The endocannabinoid system targeting drugs are an important source of candidates and have already been proposed for the treatment of schizophrenia[99,100] and mood disorders[101]. Endocannabinoid targeting drugs effective in reducing abdominal obesity have been identified[102]. More specifically, these drugs act through CB1 receptor inverse agonism. Unfortunately, marketing of the first drug, rimonabant, was discontinued for psychiatric side-effects, namely inducing depressive states and suicidal ideas[103,104]. However, newer cannabinoid compounds are emerging and a strong influence on appetite, metabolism and energy homeostasis is consistently reported[105-107]. Most importantly, preclinical studies are constantly widening the range of new candidate molecules[108-110].

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