Review

Metabolic syndrome and obesity among users of second generation antipsychotics: A global challenge for modern psychopharmacology

Leonel E. Rojo a,∗, Pablo A. Gaspar b, c, H. Silva c, L. Risco c, Pamela Arena a, Karen Cubillos-Robles a, Belen Jara a

Article info

Article history:
Received 16 June 2015
Received in revised form 21 July 2015
Accepted 21 July 2015
Available online 26 July 2015

Keywords:
Second generation antipsychotics
Diabetes
Insulin resistance
Obesity
Schizophrenia
Metabolic syndrome

Abstract

Second generation antipsychotics (SGAs), such as clozapine, olanzapine, risperidone and quetiapine, are among the most effective therapies to stabilize symptoms schizophrenia (SZ) spectrum disorders. In fact, clozapine, olanzapine and risperidone have improved the quality of life of billions of SZ patients worldwide. Based on the broad spectrum of efficacy and low risk of extrapyramidal symptoms displayed by SGAs, some regulatory agencies approved the use of SGAs in non-schizophrenic adults, children and adolescents suffering from a range of neuropsychiatric disorders. However, increasing number of reports have shown that SGAs are strongly associated with accelerated weight gain, insulin resistance, diabetes, dyslipidemia, and increased cardiovascular risk. These metabolic alterations can develop in as short as six months after the initiation of pharmacotherapy, which is now a controversial fact in public disclosure. Although the percentage of schizophrenic patients, the main target group of SGAs, is estimated in only 1% of the population, during the past ten years there was an exponential increase in the number of SGAs users, including millions of non-SZ patients. The scientific bases of SGAs metabolic side effects are not yet elucidated, but the evidence shows that the activation of transcriptional factor SRBP1c, the D1/D2 dopamine, GABA2 and 5HT neurotransmitters are implicated in the SGAs cardiovascular toxicity. Polypharmacological inter-
ventions are either non- or modestly effective in maintaining low cardiovascular risk in SGAs users. In this review we critically discuss the clinical and molecular evidence on metabolic alterations induced by SGAs, the evidence on the efficacy of classical antidiabetic drugs and the emerging concept of antidiabetic polyphenols as potential coadjuvants in SGA-induced metabolic disorders.

© 2015 Elsevier Ltd. All rights reserved.

Contents

1. Introduction ........................................................................................................ 75
2. Peculiarities of SGAs-induced metabolic syndrome ........................................ 75
3. Pathophysiology of SGAs-induced lipid accumulation and weight gain ......................................................................................... 79
4. Prophylactic interventions against SGAs-induced metabolic syndrome ........ 80
5. The emerging concept of antidiabetic polyphenols ........................................ 82
6. Concluding remarks .......................................................................................... 82
Conflict of interest ............................................................................................ 82
Acknowledgments .............................................................................................. 82
Appendix A. Supplementary data ...................................................................... 82
References ............................................................................................................ 82

* Corresponding author at: Universidad Arturo Prat, Av. Arturo Prat #2120, Iquique, Chile.
E-mail address: leonelrojo@gmail.com (L.E. Rojo).

http://dx.doi.org/10.1016/j.yphrs.2015.07.022
1043-6618/© 2015 Elsevier Ltd. All rights reserved.
1. Introduction

Second-generation antipsychotics (SGAs), clozapine, olanzapine and risperidone, have improved quality of life of billions psychiatric patients worldwide and became essential in the clinical guidelines for treatment of schizophrenia (SZ) [3,44]. Although the primary target of this drugs are SZ patients, estimated in 1% of world population [40,39], leading experts have warned on the exponential increase of the "off-label" applications of SGAs, which include non-SZ adults [75], adolescents and children [86] suffering from a wide range of psychiatric conditions [127]. Intriguingly, several of the increasing off-label indications in non-SZ patients still lack sufficient safety – and efficacy – evidence. This prescription trend might be explained by the unmet need for affordable and efficacious drugs against DSM-IV-TR categorized disorders [33], and by the intensive marketing strategies of the pharmaceutical industry. In fact, US government has fined pharmaceutical companies for the promoting some off-label uses of SGAs [103] because it was considered, not only misleading, but also dangerous for public health [74]. Some SGAs can control positive and negative symptoms of SZ within 6 weeks of use, but they also induce cardiometabolic alterations, which lead to increased morbi-mortality [31], in as short as three months after initiation of the pharmacotherapy [3]. In 2003, the FDA intended to prevent these side effects by requiring all second generation antipsychotic agents to include warning labels regarding the increased risks of diabetes mellitus and severe hyperglycemia [43]. However, recent studies showed that SGAs-induced cardiovascular diseases (CVD) are still responsible for the increased cardiovascular risk of SZ patients [83,72] and for up to 30% of the excess mortality associated with SZ[141]. A recent Meta-analysis revealed that the risk for metabolic syndrome among SZ patients is higher than that of non-SZ individuals and clozapine treatment increases cardiovascular risk of SZ patients [77]. Another Meta-analysis concluded that patients with bipolar treated with antipsychotic display a higher risk of metabolic syndrome than their antipsychotic free counterparts [125].

The group of SGAs includes drugs with different chemical structures, mode of action and risk profile for metabolic side effects, being olanzapine the most toxic drug of this group followed by clozapine, risperidone, quetiapine and aripiprazole [130,31]. Clozapine was launched to market in 1990, with the bizarre retail price of US$8,444 per year treatment, a high risk of accelerated weight gain [23] and warnings of potential agranulocytosis [22]. This astonishing high cost of clozapine included a blood test only performed the manufacturer’s personnel [129]. In spite of its cost and serious side effects, the annual sales of clozapine increased up to US$500 million/year in the first ten years, while risperidone reached three times those of clozapine in its first 5 years in the market. Olanzapine, the most unsafe drug (for cardiometabolic side effects), reached around US$ 2,500 million/years in its first ten years in the market and it continues to grow to date [22]. In Chile, according to the official records of the Chilean National Institute of Public Health (ISP), there is a similar trend with increasing annual imports of clozapine and olanzapine during the past 9 years (Fig. 1). Since 2011, the prescription trends in the US are moving toward safer antipsychotics, such as quetiapine, aripiprazole and ziprasidone [67], but the elevated cost of these drugs limits their availability for the majority of SZ patients. For example, in Chile, aripiprazole is not included in the medications that are available through the public health system for SZ patients. Thus, like in the rest of the world, most of SZ patients in Chile continue as a group at high risk for metabolic syndrome (MetS) [72].

The pathophysiology of the SGAs-induced alterations has not been fully elucidated, but increased food intake, weight gain, hyperglycemia, lipid accumulation in adipose cells and liver are hallmarks of this problem [1,11]. The current evidence show that the integration of the appetite regulation signals in the Arcuate Nucleus is impaired by SGAs, such as olanzapine and clozapine, which results in hyperphagia [1]. Clozapine-induced hyperphagia is reversed by i.p. injection of dopamine D1 and D2 antagonists and 5-HT1B, 5-HT2 and 5-HT3 agonists in mice [60] and also by fluoxetine, a serotonin reuptake inhibitor. Unfortunately, the protective effect displayed by fluoxetine had little clinical significance, as it was not reproduced in humans [89]. Prevention strategies based on genomic analyzes are emerging as a possible answer to this problem. For example, the GABA2 receptor polymorphism was suggested as a good predictor of weight gain in SGAs-treated patients [137]. Recent studies have shown that SGAs-induced insulin resistance, weight gain and lipid accumulation are associated with the up regulation of sterol regulatory element-binding protein 1c (SREBP1c) [38,135,53]. This finding has opened new molecular targets for prophylactic drugs. SRBP1c is a master regulator of lipid biosynthesis in liver and fat tissue (Qui et al., 2005) and its inhibition was successful in ameliorating SGAs-induced lipid accumulation cellular and animal models [53]. So far, the life style modifications, nutritional consulting, and polypharmacological interventions have proved limited efficacy against SGAs-induced MetS (Table 1). Our group has received a federal grant from the Chilean government to search for new pharmacological agents against SGAs-induced adipogenesis based on selected molecules derived polyphenols with insulin sensitizing properties [95,100,98,118]. Which is supported by a growing body of evidence, including recent clinical trials [28,101]. Our group and others have demonstrated that specific polyphenols from dietary sources ameliorate insulin resistance [100,98,71,107,64], inflammation [121,107] and obesity [34,108]. Anthocyanins, a family polyphenols, have shown significant clinical effect in improving insulin sensitivity in obese, non-diabetic, insulin-resistant patients [115]. Berberine is also an example of an anti-diabetic phytochemical with potential protective effect against lipid accumulation induced by clozapine [53]. The present review analyze the recent progress in understanding the SGAs induced metabolic alterations, and the rational for developing therapeutic agents based on anti-diabetic anti-obesity drugs and dietary polyphenols.

2. Peculiarities of SGAs-induced metabolic syndrome

In general population full-blown type II diabetes and morbid obesity takes up to 5–10 years to unfold [109]. In the case of type 2 diabetes, a pre-diabetic stage characterized by insulin resistance, hyperinsulinemia and progressive pancreatic dysfunction, can asymptptomatically develop over several years before diabetes is clinically diagnosed [109]. Conversely, in SAG-treated subjects, the process from low – or completely absent – cardiovascular risk to full-blown diabetes and/or morbid obesity is significantly shorter, ranging from 6 to 12 weeks up to 12 months (Fig. 2) [61]. This prodromal period will depend upon the specific antipsychotic drug used and the individual genetic background. Most of SGA-treated patients will gain and maintain high weight and insulin resistance for long time, even after changes in life style and/or use of anti-diabetic drugs. The burgeoning literature on metabolic issues associated with the use of SGAs [47,130,110,15,3] has increased opportunities for the rational development single-target prophylactic agents, which can protect physical health and improve compliance of patients treated with SGAs [141,130]. A careful selection of the specific SGA is important for risk/benefit evaluation, since clozapine and olanzapine are known to cause the most severe profile of metabolic side effects [110], while quetiapine, aripiprazole and ziprasidone display significantly lower risk of metabolic alterations [72]. The most prevalent manifestations of MetS in clozapine and olanzapine-treated patients are weight
Table 1
Summary of preclinical and clinical studies assessing interventions against SGAs-induced metabolic alterations.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>SD</th>
<th>N</th>
<th>Dur</th>
<th>PD</th>
<th>SO</th>
<th>Results</th>
<th>MC +/-</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin 750 mg/day</td>
<td>Double-blind, placebo-controlled</td>
<td>40</td>
<td>3</td>
<td>Changes of weight, BMI, WC, waist-to-hip ratio, fasting glucose, fasting insulin, proportion of patients with &gt;7% weight gain at 3 months, insulin resistance index</td>
<td>Changes in SAPS and SANS scores and adverse effects</td>
<td>Treatment with metformin in patients treated with OLZ decreased body mass index and weight gain, no changes in insulin levels and insulin resistance</td>
<td>Positive</td>
<td>[93]</td>
</tr>
<tr>
<td>Metformin 850–1750 mg/day</td>
<td>Double-blind placebo-controlled trial</td>
<td>40</td>
<td>3.5</td>
<td>Body weight gain, HOMA-IR</td>
<td></td>
<td>Metformin decreased HOMA-IR and glucose levels. No changes in weight gain in patients treated with OLZ</td>
<td>Negative</td>
<td>[120]</td>
</tr>
<tr>
<td>Metformin 500–850 mg</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>39</td>
<td>4</td>
<td>Prevention of further weight accumulation from atypical antipsychotics</td>
<td></td>
<td>Metformin ameliorated weight gain, insulin resistance and improved abnormally high glucose levels in children treated with olanzapine, risperidone, or quetiapine</td>
<td>Positive</td>
<td>[30]</td>
</tr>
<tr>
<td>Metformin 850–2250 mg/day</td>
<td>Multicentric, double-blind, placebo-controlled trial</td>
<td>80</td>
<td>4</td>
<td>Weight loss (body weight, BMI, WC)</td>
<td></td>
<td>Metformin group decreased weight and leptin levels, but did not improve lipid profile and levels of Hb1c in OLZ treated patients</td>
<td>Positive</td>
<td>[13]</td>
</tr>
<tr>
<td>Metformin 750 mg/day</td>
<td>Randomized controlled trial</td>
<td>128</td>
<td>24</td>
<td>Changes of weight, BMI, waist circumference, fasting glucose, fasting insulin level, and insulin resistance index</td>
<td>Change in PANSS total scores and adverse effects</td>
<td>Metformin was modestly superior to life style regarding the prevention of weight gain, insulin resistance and increase in BMI. Life style modification-plus-metformin was superior to metformin alone. OLZ-Nizatidine patients had less weight gain versus the placebo. Nizatidine was well tolerated and is estimated to have a temporary early effect in the low weight gain, but it is diminished after 16 weeks.</td>
<td>Positive</td>
<td>[133]</td>
</tr>
<tr>
<td>Nizatidine 150 mg b.i.d. or 300 mg b.i.d.</td>
<td>Double-blind placebo-controlled trial</td>
<td>175</td>
<td>4</td>
<td>Weight gain</td>
<td></td>
<td>Decrease in weight gain and leptin levels but below the level for statistical significance.</td>
<td>Negative</td>
<td>[19]</td>
</tr>
<tr>
<td>Nizatidine (150 mg b.i.d.)</td>
<td>Double-blind and placebo-controlled trial</td>
<td>47</td>
<td>2.5</td>
<td>Weight gain</td>
<td>PANSS score, leptin levels and BMI</td>
<td>Negative</td>
<td>[7]</td>
<td></td>
</tr>
<tr>
<td>Nizatidine 5–25 mg 15.3 mg/day</td>
<td>Double-blind and placebo-controlled trial</td>
<td>59</td>
<td>3</td>
<td>Weight gain</td>
<td>Plasma leptin levels, BMI, PANSS scores</td>
<td>Positive</td>
<td>[6]</td>
<td></td>
</tr>
<tr>
<td>Orlistat</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>71</td>
<td>4</td>
<td>Weight gain</td>
<td></td>
<td>Mild decrease in weight gain in male treated with OLZ and CLO, no effect in women</td>
<td>Positive</td>
<td>[56]</td>
</tr>
<tr>
<td>Sibutramine 15 mg/day</td>
<td>Double-blind, Placebo-controlled Trial</td>
<td>37</td>
<td>3</td>
<td>Weight gain</td>
<td>Waist circumference, body mass index, and hemoglobin A1c</td>
<td>Decreased in weight gain, waist circumference, body mass index, and hemoglobin A1c in schizophrenia patients treated with OLZ</td>
<td>Positive</td>
<td>[48]</td>
</tr>
<tr>
<td>Ranitidine 600 mg/day</td>
<td>Randomized triple blind controlled trial</td>
<td>52</td>
<td>4</td>
<td>BMI</td>
<td></td>
<td>Ranitidine induced less weight gain in OLZ-treated patients than the control group, but only in the first two months</td>
<td>Negative</td>
<td>[92]</td>
</tr>
<tr>
<td>Reboxetine 4 mg/d with betahistine 48 mg/day</td>
<td>Randomized double-blind study</td>
<td>26</td>
<td>1.5</td>
<td>Weight gain</td>
<td></td>
<td>Reboxetine decreased number of patients with &gt;7% weight gain in schizophrenic OLZ-treated. Small number of patients makes challenging to reach decisive conclusions.</td>
<td>Positive</td>
<td>[88]</td>
</tr>
<tr>
<td>Drug/Metabolite</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>BMI Change</td>
<td>Reactions/Findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>-------------</td>
<td>------------</td>
<td>--------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reboxetine 4 mg/day</td>
<td>Double-blind placebo-controlled study</td>
<td>60</td>
<td>1.5</td>
<td>Weight gain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate 100 mg/d</td>
<td>Randomized double-blind placebo controlled study</td>
<td>66</td>
<td>3</td>
<td>Weight gain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Famotidine 40 mg/day</td>
<td>Double-blind placebo-controlled pilot study</td>
<td>14</td>
<td>1.5</td>
<td>Body weight and BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone 4–8 mg/day</td>
<td>Pilot double-blind, placebo-controlled</td>
<td>30</td>
<td>3</td>
<td>Weight gain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone 4 mg/day</td>
<td>Double Blind, Placebo-Controlled Trial</td>
<td>18</td>
<td>2</td>
<td>SG (plasma glucose clearance irrespective of the action of insulin), SI (insulin sensitivity)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine 300 mg/day</td>
<td>Double-blind, placebo-controlled</td>
<td>21</td>
<td>3</td>
<td>Body weight and BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine 100–300 mg/day</td>
<td>Randomized, double-blind</td>
<td>125</td>
<td>6</td>
<td>Body weight and BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine 20 mg/day</td>
<td>Double-blind, placebo-controlled</td>
<td>30</td>
<td>2</td>
<td>Body weight and BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resveratrol 10 mg/kg/day</td>
<td>Study animals</td>
<td>18</td>
<td>0.6</td>
<td>Non pharmacological therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green tea and conjugated linoleic acid</td>
<td>Case control</td>
<td>4</td>
<td>6</td>
<td>Weight gain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin 300 mg/kg and berberine 380 mg/kg/day</td>
<td>Study animals</td>
<td>48</td>
<td>0.5</td>
<td>Body weight body fat mass, body fat percentage, lean body mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular in vitro study</td>
<td>Weight gain and adiposity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Schizophrenic patients treated with OLZ in combination with reboxetine had less weight gain compared to the control group.
Topiramate decreased BMI, weight, and waist circumference. Hip-to-waist ratio did not change in SGAs-treated patients.
Famotidine did not prevent weight gain in schizophrenic patients treated with OLZ.
Rosiglitazone increased weight and decreased insulin levels and HOMA-IR in OLZ-treated patients.
Rosiglitazone-treated patients had a reduction in LDL-C, a non-significant improvement in SI and SG. Partial improvement of insulin resistance and hypercholesterolemia in patients treated with clozapine.
Amanitadine-treated patients showed less weight gain relative to controls, no changes in the levels of insulin, glucose, leptin, prolactin and lipid levels.
The OLZ-amantadine treatment was tolerated by patients and achieved a reduction in weight gain compared to placebo-OLZ group.
Patients treated with OLZ-Fluoxetine showed no significant differences from the control group, so it is concluded that co-administration of these drugs does not reduce weight gain.
Non pharmacological therapy
Resveratrol-plus-olanzapine-group displayed less weight gain than the group treated with olanzapine alone.
Green tea decreased the percentage of body fat and increased lean body mass with the use of the tea extract.
Metformin and berberine decreased weight gain and white fat accumulation induced by OLZ in rats. Metformin did not change brown adipose tissue.

**Dur:** duration of the study (months), **Intervention result:** positive (+) and negative (−); **N:** number of patients, **PO:** main primary outcomes or biological effects, **SO:** main secondary outcomes, **WC:** waist circumference, **BMI:** body mass index, **MC:** main conclusion, **PANSS:** positive and negative syndrome scale, **BWG:** body weight gain, **OLZ:** olanzapine, **CLO:** clozapine.
Fig. 1. Annual imports of second generations antipsychotics in Chile. The graphs shows the annual imports for clozapine (A), olanzapine (B), and risperidone (C) from 2006 to 2014. The data were obtained from official records of The Chilean National Institute of Health (ISP) report N °AO005W0003432.

gain [72,63], hypertriglyceridemia [3], and insulin resistance [66]. There is a positive correlation between the administration of SGAs and hepatic steatosis in – 12–24 h after i.p. injection in rats [55] and the gene expression of profiles follow a biphasic pattern for PPAR controlled genes that leads to rapid accumulation of triglycerides, phospholipids, and cholesterol in the liver [38]. The obesity induced by clozapine is seemingly affected by genetic polymorphisms and it is followed by an increase in plasma leptin of five folds over baseline [4,17,55,112]. Thus, although few studies argue otherwise [45,110], the vast majority of published literature [47,55,82,16], including a recent clinical trial [130], supports the hypothesis that, independent of baseline BMI and the presence/absence of MetS, clozapine and olanzapine induce accelerated obesity, hyperglycemia and hypertriglyceridemia [38]. The current evidence also shows that SGAs-induced MetS is mediated by four biological phenomena: (i) Changes in adipocyte differentiation markers [84], (ii) Induction of lipid biosynthesis/accumulation in liver and fat tissue [60,63,110], (iii) the up-regulation of the sterol regulatory element-binding protein (SREBP) in adipocytes and liver cells [53,136], and (iv) Hyperphagia associated to altered appetite controlling signals regulated by POMC, CART, D2, 5HT2 and H1 [65,46,94] in the hypothalamus and M3 muscarinic receptors in peripheral tissues [94]. Hepatic steatosis [138] is among the most prevalent risk factors found in patients treated with SGAs, especially for those naïve to treatment, in which SGAs cause a more noticeable increase in weight compared with chronically treated patients [132]. The SGAs-induced metabolic disturbances were associated with biphasic patterns of lipid-related genes in the liver and in white adipose tissue depots [55]. In addition to genetic and pharmacological factors, SZ patients are at risk for developing obesity due to behavioral factors including inactive lifestyle, length of the disease [77], poor dietary choices, and smoking [3].
SAGs-induced MetS can be aggravated by factors like, ethnicity, advanced age, and female sex. Adiponectin is one of the most important adipocytokines, it shows sexual dimorphism, which may explain why the risk of SGA-induced cardiometabolic alterations in females is higher than in males [61]. Polymorphisms in the hormone adiponectin are also associated with SGA-induced cardiometabolic abnormalities [114].

Interestingly, the efficacy of SGA in reducing positive symptoms shows a negative correlation with the appearance of the MetS in drug naive schizophrenia patients [126]. The mechanisms of this correlation are yet to be elucidated, but studies on the role of H1 and HFT antagonism [114], and expression of leptin and adiponectin [84,130] are providing the first clues to solve this puzzle. Environmental and/or epigenetic factors also contribute to the propensity to develop metabolic syndrome in SAGs-treated patients. For example, the ADRA2A polymorphism is present in European descendants, but not in African descendants. This polymorphism seemingly functions as a risk predictor for clozapine-/olanzapine-induced weight, because the carriers of the C allele gain more weight compared with the subjects homozygous for the G allele [112]. Regardless of baseline BMI, ethnicity [77] and initial body fat mass, the advanced age, and female gender are more relevant in the clinical manifestation of SAGs side effects, as the female SGA-treated patients had a higher incidence of diabetes compared with the general population [66].

3. Pathophysiology of SAGs-induced lipid accumulation and weight gain

Cellular and animal studies have established that clozapine increases lipogenesis through the up-regulation of SREBP1c [55,113,136], this transcriptional factor is a major regulator of the lipid biosynthesis in liver and adipose tissue [80]. There are two SREBP isoforms, SREBP1 and SREBP2, encoded by two different genes, SREBP1 has two splice variants, SREBP1a and SREBP1c [80]. SREBP1a is a ubiquitous protein that regulates genes in both cholesterol and fatty acid biosynthesis [111]. While SREBP1c – and its target genes ACL, ACC1, ACC2, FANS, SCD1, GPAT, lipine, adiponectin – are involved in the biosynthesis of triglycerides and in peripheral tissues. The overexpression of SREBP1c can cause pronounced metabolic disturbances [24], as it was demonstrated by the overexpression SREBP1 in rodents that developed hepatic steatosis and severe insulin resistance [91]. These findings brought the testable hypothesis that SREBP1c inhibitors, like Berberine, can function as protective agents against SAGs-induced lipid accumulation in liver and adipose tissue [53,128,135]. Lipoprotein lipase (LPL) is another key player in the SAGs-induced alterations of lipid metabolism (Fig. 2). LPL is involved in triglyceride hydrolysis and the transport of free fatty acids [38]. It also mediates the hydrolysis of triglycerides in liver and adipocytes. LPL is inhibited by clozapine in vivo and in vitro [136]. Clozapine-induces elevation of free fatty acids and glucose in serum [1] and hepatic accumulation of lipids in female Sprague–Dawley rats [38]. Hyperphagia is another major contributor to weight gain among SAGs users [1,60]. The evidence suggest that the increase olanzapine-induced hyperphagia might be secondary to the activation of SREBP1c-controlled genes, like PPARγ [37,2,134,117,79], FASN [119,134] and LDLR [134]. We believe that the overexpression of LDLR also results in an augmented capacity of adipocytes to accumulate cholesterol (Fig. 3). Olanzapine decreases the expression of 5-lipoxygenase-activating protein (FLAP) [35], FLAP is an enzyme involved in the production of leukotriene. Thus, it is not clear how FLAP contributes to SAGs-mediated cardiovascular risk, because leukotriene are known to mediate pathological inflammation in different tissues [35]. Olanzapine also increases levels of adiponectin and leptin, through SREBP1c 1 [134,96,106]. Adiponectin and leptin are associated with appetite control in the arcuate nucleus of the hypothalamus (Fig. 3) [96]. Leptin levels are inversely correlated with appetite [96,139]. However, plasma levels of leptin in obese individuals patients are elevated [96] which led to the concept of central “leptin resistance” [81]. We hypothesized that this phenomena is also present in SGAs-treated patients (Fig. 3), as they also exhibit elevated plasma levels of leptin [63,65,105,68]. Leptin receptors inhibit appetite through the STAT3/Pi3K pathway in POMC neurons [139] of the arcuate nucleus. During leptin resistance POMC neurons activate the SOCS5 signaling, which results in inhibition of satiety and increased food intake [139,78]. It is not yet clear how POMC and CART signal are impaired by SAGs, however, the hypothesis of multifaceted mechanism triggered by SGAs [21], both at peripheral and hypothalamic levels, seems as an attractive model to explain this puzzle.

4. Prophylactic interventions against SAGs-induced metabolic syndrome

In Table 1, we summarized the results of 20 clinical studies and three preclinical studies, assessing the efficacy of pharmacological interventions (i.e., metformin, nizatadine, orlistat, ranitidine, topiramate, etc.) against SGA-induced metabolic side effects. This summarized evidence shows that one out of five studies with metformin resulted in negative results. The other four positive studies concluded that weight gain, insulin resistance can be efficiently controlled, but lipid profile may even worsen. Metformin reduced body weight in clozapine-treated patients [25], but its beneficial effects disappeared after discontinuing this medication. Orlistat in overweight/obese clozapine–or olanzapine-treated patients failed to prevent obesity and lipid accumulation [56], which suggest that the intestinally absorbed lipids may not be relevant for SGAs-induced obesity. Atomoxetine, a selective norepinephrine reuptake inhibitor with appetite suppressant activity, was not effective in preventing obesity in patients treated with olanzapine and clozapine [9].

Clinical and molecular data supports the hypothesis that SGAs-induced weight gain and hyperglycemia are part of a multifactorial problem, which makes it difficult to tackle with a single-drug therapy [4]. The therapies based on antagonism of hypothalamic dopamine D1/D2 and H1 receptors still awaits for clinical sup-
porting data [46,60]. Respect to the serotonergic hypothesis, the interventions with fluoxetine also failed. The use of sertraline in clozapine-induced weight gain resulted in cardiac death [50]. The tetradecylthioacetic acid (TTA), a modified fatty acid, recently showed a minor protective effect against hypertriglyceridemia, but failed to prevent weight gain induced by clozapine in rodents [113]. Berberine, a natural alkaloid, inhibited in vitro adipogenesis and SREBP-1 overexpression induced by clozapine and risperidone in 3T3 adipocytes [53]. As shown in Table 1, resveratrol and green tea, showed some efficacy in decreasing weight gain and fat mass accumulation induced by olanzapine in rodents.

5. The emerging concept of antidiabetic polyphenols

Polyphenols are family of polar compounds found in fruits and vegetables, they have been popular for their potent antioxidant effect, but in the past 5 years increasing evidence has shown that, anthocyanins, a specific category of polyphenols, are effective in ameliorating obesity [108,70,57] and insulin resistance [76,42]. In Table 2, we summarized the main clinical and pre-clinical evidence in this area. The mode of action and pharmacokinetic profile of these compounds is not yet fully elucidated and their bioavailability after oral administration is a matter of continuous controversy [71]. However, there is robust evidence on their efficacy in cardiometabolic problems [20,131]. Kurimoto et al. reported that anthocyanins from black soy bean increased insulin sensitivity via the activation of AMP-activated protein kinase (AMPK) in skeletal muscle and liver of in type 2 diabetic mice [64]. AMPK, a regulator of glucose and lipid metabolism in liver and muscle cells, is inhibited by olanzapine, which may contribute to the olanzapine-induced hepatic lipid accumulation [85]. Anthocyanins also display insulin-like effects even after intestinal biotransformation [71]. Our laboratory has started a new project funded by the Chilean federal agency CONICYT, to elucidate the effect of polyphenols on SGAs-induced lipid accumulation in liver and adipocytes. We expect that by the end of this program we will have clinical evidence to help SGAs treated patients. We also aim to have a better understanding of the biochemistry and pharmacology of SGAs-induced lipid accumulation and the prophylactic role of specific polyphenols.

We have previously demonstrated that anthocyanins ameliorate signs of diabetes and metabolic syndrome in obese mice fed with a high fat diet have [100,98,71,27]. Delphinidin 3-sambubioside-5-glucoside (D3S5G), an anthocyanin from Aristotelia chilensis, is as potent as metformin in decreasing glucose production in liver cells, and it displays insulin-like effect in liver and muscle cells [98]. The anti-diabetic mode of action of anthocyanins have been associated with the transcriptional down-regulation of the enzymes PEPCK and G6P gene in hepatocytes [100,98]. Prevention of adipogenesis is also another reported mechanism for some anthocyanins from A. chilensis [108]. Anthocyanins also induce significant increase in circulating levels of adiponectin in murine models of MetS [124,123]. This is relevant, since adiponectin is reduced in clozapine-treated patients and weight reduction is associated with higher circulating levels of adiponectin. In a recent study Roopchand et al., demonstrated that blueberry anthocyanins are as potent as metformin in correcting hyperglycemia and obesity in obese hyperglycemic mice [98,100]. Dietary anthocyanins have also proven efficacy in decreasing levels of the inflammatory mediators PAI-1 and retinol binding protein 4 in obesity and type 2 diabetes [121,107]. Recent medical and
Table 2
Clinical trials assessing efficacy of polyphenols in diabetes, obesity and metabolic syndrome.

<table>
<thead>
<tr>
<th>Polyphenols/dosage</th>
<th>Study design</th>
<th>N (beginning/end)</th>
<th>Duration</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
<th>Results and comments</th>
<th>Overall conclusion</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinnamon extract/250 mg, twice a day</td>
<td>Randomized double-blind, placebo controlled study</td>
<td>173/137</td>
<td>10 weeks</td>
<td>Fasting serum glucose</td>
<td></td>
<td>Decreased glucose, fasting insulin, LDL and HDL in the supplemented group with cinnamon extract, extract compared to placebo</td>
<td>Positive</td>
<td>[5]</td>
</tr>
<tr>
<td>Fresh pomegranate juice/1.5 mL/kg, Purified anthocyanin/320 mg/d</td>
<td>Randomized study</td>
<td>85</td>
<td>3 h</td>
<td>Fasting serum glucose and insulin Total cholesterol, HDL-cholesterol, LDL-cholesterol and triacylglycerol Body weight, BMI, body composition, resting energy expenditure, and substrate oxidation were measured at baseline</td>
<td>Serum inflammatory markers</td>
<td>Decreased insulin resistance, FSG and increased B cell function Anthocyanin mixture reduced the inflammatory response, serum CRP, VCAM-1 and IL-1b in hypercholesterolemic subjects</td>
<td>Positive</td>
<td>[10]</td>
</tr>
<tr>
<td>Pomegranate juice 50 mL/day</td>
<td>Unspecified</td>
<td>20</td>
<td>15 weeks</td>
<td>The body weight (BW), body mass index (BMI) and waist circumference (WC)</td>
<td>Blood glucose, creatinine, aminotransferases aspartate, aminotransferases alanine, uric acid, and plasma lipoproteins (triglyceride, cholesterol, HDL-cholesterol (HDL) and LDL-cholesterol (LDL)</td>
<td>Antioxidant effects in diabetic patients No significant differences in BW, BMI and WC between the control group and the group treated with GTE. Significant reduction in LDL-cholesterol and triglycerides, increase HDL-cholesterol, adiponectin and ghrelin Reduced diastolic blood pressure and increased total antioxidant potential type 2 diabetes mellitus</td>
<td>Negative</td>
<td>[102]</td>
</tr>
<tr>
<td>Green tea/250 mg, three times a day</td>
<td>Randomized, controlled clinical trial</td>
<td>78/100</td>
<td>12 weeks</td>
<td>Fasting plasma glucose and insulin</td>
<td>HbA1c, lipid peroxidation, high-sensitivity C-reactive protein, antioxidant status, cytokines</td>
<td>Decreased malondialdehyde, protein carbonyls. Increased GSH levels</td>
<td>Positive</td>
<td>[51]</td>
</tr>
<tr>
<td>Raisins (Vitis vinifera) 36 g/day</td>
<td>Randomized controlled trial</td>
<td>48</td>
<td>24 weeks</td>
<td>Blood pressure, fasting glucose Total antioxidative capacity (TAC), levels of malondialdehyde, protein carbonyls (CARB) (GSH), catalase activity</td>
<td>Plasma lipoproteins, apolipoproteins, adipokines</td>
<td>Decrease plasmatic insulin, lipoprotein and HOMA-IR, increased HDL, apolipoprotein AI and A-II Decreased aspartate aminotransferase, glucose, alanine aminotransferase, total cholesterol, TNFα cytoketarin and fibroblast growth factor. Elevated adiponectin</td>
<td>Positive</td>
<td>[29]</td>
</tr>
<tr>
<td>Green tea (Camellia sinensis)</td>
<td>Randomized controlled trial</td>
<td>35</td>
<td>8 weeks</td>
<td>Parameters, of metabolic syndrome</td>
<td></td>
<td>No change in metabolic syndrome features, a decrease in plasma amyloid alpha</td>
<td>Negative</td>
<td>[14]</td>
</tr>
<tr>
<td>Whole blueberries 22.5 g, twice a day</td>
<td>Double-blind, randomized, placebo-controlled clinical study</td>
<td>32</td>
<td>6 weeks</td>
<td>Insulin sensitivity, inflammatory biomarkers, and adiposity</td>
<td>Body weights</td>
<td>Improved insulin sensitivity with cranberry, no changes in inflammatory biomarkers, adiposity and energy intake</td>
<td>Positive</td>
<td>[116]</td>
</tr>
<tr>
<td>Purified anthocyanins 160 mg twice a day</td>
<td>Randomized, double-blind trial</td>
<td>58</td>
<td>24 weeks</td>
<td>Serum lipids, fasting plasma glucose, insulin, and glycated hemoglobin</td>
<td>Oxidative stress markers, plasma concentrations of 8-isoprostaglandin</td>
<td>Decreased LDL cholesterol, triglycerides, apolipoprotein, and apoC-III and increased HDL Decreased glucose, levels in type 2 diabetes patients.</td>
<td></td>
<td>[69]</td>
</tr>
</tbody>
</table>
nutritional studies suggest that anthocyanins from diverse dietary sources are potent anti-diabetic, anti-obesity and cardioprotective molecules [57,100,99,27,36]. Another fact that makes anthocyanins candidates for preventing clozapine-induced lipogenesis is that they are capable of suppressing the inflammatory response through targeting the phospholipase A2, PI3K/Akt and NF-kappaB pathways, [34]. These pre-clinical findings were corroborated by clinical evidence showing the dietary anthocyanins from blueberries improve insulin resistance in young obese, non-diabetic adults [115]. The clinical efficacy of polyphenols in SGAs-induced MetS has not yet been established, but a recent pre-clinical demonstrated that, resveratrol, a polyphenol found in grapes, decreases olanzapine-induced weight gain [104].

6. Concluding remarks

In China, as in the rest of the world, the use of SGAs is increasing, as they provide a powerful therapeutic alternative to control symptoms of SZ patients and non SZ patients. Especially those with severe acute psychotic syndromes. However, given the known cardiometabolic complications, there is a need for affordable prophylactic agents because the newer – and safer – atypical antipsychotics are not yet available to all patients due to their high cost. It is necessary to continue the basic and clinical research on new prophylactic agents, such as D1, H1 ligands, the retinoid ligand AM-80 [97], SREBP1 inhibitors, to further understand their potential for ameliorating SGAs side effects. The current literature suggest that mechanisms of SGAs-induced metabolic syndrome involves at least two separate systems: the peripheral lipid and glucose metabolism, controlled by SREBP1 transcriptional factor, and the alteration of appetite control in the hypothalamus through neurons of the arcuate nucleus. We believe that a better understanding of the antiadipetic effect of specific polyphenols will help us to find new – and affordable – treatments for this medical problem.

Conflict of interest

Authors of this manuscript do not have conflicting interest in regard with the manuscript.

Acknowledgments

This work was funded by Proyecto Fondecyt Iniciación N°11140915 of CONICYT, Chile and Universidad Arturo Prat.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [http://dx.doi.org/10.1016/j.phrs.2015.07.022](http://dx.doi.org/10.1016/j.phrs.2015.07.022)

References


85


