Impaired hormonal regulation of appetite in schizophrenia: A narrative review dissecting intrinsic mechanisms and the effects of antipsychotics

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Abstract
Cardiometabolic diseases are the main contributor of reduced life expectancy in patients with schizophrenia. It is now widely accepted that antipsychotic treatment plays an important role in the development of obesity and its consequences. However, some intrinsic mechanisms need to be taken into consideration. One of these mechanisms might be related to impaired hormonal regulation of appetite in this group of patients. In this narrative review, we aimed to dissect impairments of appetite-regulating hormones attributable to intrinsic mechanisms and those related to medication effects. Early hormonal alterations that might be associated with intrinsic mechanisms include low levels of leptin and glucagon-like peptide-1 (GLP-1) together with elevated insulin levels in first-episode psychosis (FEP) patients. However, evidence regarding low GLP-1 levels in FEP patients is based on one large study. In turn, multiple-episode schizophrenia patients show elevated levels of insulin, leptin and orexin A together with decreased levels of adiponectin. In addition, patients receiving olanzapine may present with low ghrelin levels. Post mortem studies have also demonstrated reduced number of neuropeptide Y neurons in the prefrontal cortex of patients with schizophrenia. Treatment with certain second-generation antipsychotics may also point to these alterations. Although our understanding of hormonal regulation of appetite in schizophrenia has largely been improved, several limitations and directions for future studies need to be addressed. This is of particular importance since several novel pharmacological interventions for obesity and diabetes have already been developed and translation of these developments to the treatment of cardiometabolic comorbidities in schizophrenia patients is needed.

1. Introduction
Schizophrenia is one of severe neurodevelopmental disorders and often leads to considerable functional impairment. The typical onset of schizophrenia tends to appear in the late adolescence or early adulthood and usually includes positive, negative and affective symptoms as well as cognitive deficits. Notably, patients with schizophrenia frequently develop obesity, type 2 diabetes and cardiovascular diseases (Mitchell et al., 2013). These comorbidities largely contribute to reduced life expectancy in this group of patients (Laursen et al., 2011; Nordentoft et al., 2013). Previous epidemiological studies have identified several lifestyle characteristics and associated environmental factors (poor dietary habits, sedentary behaviors, cigarette smoking and early-life stress) that account for increased mortality in patients with schizophrenia (De Hert et al., 2009; Piotrowski et al., 2017). Additionally, it has clearly been shown that various medications, especially second-generation antipsychotics (SGAs), point to this phenomenon (Hirsch et al., 2017). Metabolic side effects of SGAs have largely been attributed to their interactions with serotoninergic and histaminergic receptors (Nasrallah, 2008; Siafis et al., 2017). However, there is a growing body of evidence that SGAs may also lead to metabolic disturbances via direct effects on hormonal activity of adipose tissue (Ferreira et al., 2020).

Although various environmental exposures mentioned above have been associated with cardiometabolic risk factors in schizophrenia-spectrum disorders, several studies have demonstrated that patients with early psychosis and at-risk individuals already present with subclinical or clinically relevant metabolic dysregulations. These alterations include lipid profile disturbances (Misiak et al., 2017; Pillinger et al., 2017b), hyperglycemia and insulin resistance (Greenhalgh et al., 2019).
2017; Perry et al., 2016), hyperprolactinemia (González-Blanco et al., 2016), hyperhomocysteinemia (Misiak et al., 2016), low levels of folate and B vitamins (Firth et al., 2017), higher levels of C-reactive protein (Fernandes et al., 2016; Park and Miller, 2019) and pro-inflammatory cytokines (Frydecka et al., 2018; Miller et al., 2011) as well as dys- function of the hypothalamus-pituitary-adrenal (HPA) axis activity (Hubbard and Miller, 2019; Saunders et al., 2019). Moreover, a recent meta-analysis demonstrated that drug-naïve or minimally-medicated patients with first-episode psychosis (FEP) have lower body mass index (BMI) and higher waist-to-hip ratio (WHR) compared to healthy controls (Shah et al., 2019). In addition, results of studies showing that patients with schizophrenia present with high rates of metabolic syndrome and its single components were published before the development of SGAs (Dynes, 1969). These observations have led to the hypothesis that cardiometabolic diseases and schizophrenia-spectrum disorders share overlapping genetic backgrounds. Subsequently, some studies have aimed to address this hypothesis. These studies have provided the following lines of findings: 1) patients with schizophrenia and type 2 diabetes show higher genetic predisposition to both disorders than healthy controls (Hackinger et al., 2018); 2) there is a shared genetic risk of schizophrenia and binge eating (Solmi et al., 2019); 3) a polygenic risk score for schizophrenia is associated with immune and metabolic serum markers in FEP patients (Ma et al., 2019) and 4) certain gene variants are associated with common cardiovascular risk factors and schizophrenia susceptibility (Andreasen et al., 2013).

One of potential mechanisms linking cardiovascular risk with early psychosis might be related to impaired hormonal regulation of appetite by hormones released by adipose tissue. Indeed, there is evidence that indices of increased visceral adiposity and various nutritional deficiencies are present in patients with FEP (Firth et al., 2017; Shah et al., 2019). In addition, patients with schizophrenia have significantly higher dietary energy and sodium intake than controls (Teasdale et al., 2019). Accumulating evidence indicates that hormones involved in the regulation of appetite might also be involved in the pathophysiology of psychosis. Moreover, it cannot be excluded that early alterations in hormonal regulation of appetite impact subsequent weight gain associated with the use of antipsychotics. Recognizing critical pathways related to hormonal regulation of dietary habits might hold a great promise for developing novel pharmacological approaches that aim to prevent the development of cardiometabolic comorbidities. In this narrative review, we provide insights into hormonal mechanisms that may underlie increased food intake in patients with schizophrenia and early psychosis. Furthermore, we highlight the effects of antipsychotics on the release and activity of appetite regulating hormones. Finally, we suggest that dysregulated hormonal regulation of appetite might be a novel target for interventions that aim to prevent or treat obesity-related comorbidities in patients with schizophrenia-spectrum disorders.

2. Adipose tissue and its biology – overview of physiological mechanisms

There is now a general consensus that adipose tissue is an active endocrine organ that secretes a number of bioactive peptides regulating several biological processes (Coelho et al., 2013). Apart from adipocytes, it contains blood and endothelial cells, pericytes and pre-adipocytes. Depending on developmental origins, morphological features, distribution, mitochondrial activity and gene expression patterns, it can be divided into two main types – white adipose tissue (WAT) and brown adipose tissue (BAT).

Notably, WAT is the main energy storage in the form of triglycerides, and accounts for up to 50 % of the total body weight (Ferreira et al., 2020). Morphologically, adipocytes from WAT have a large unilocular lipid droplet and few mitochondria. It is located in two depots that are represented by visceral WAT and subcutaneous WAT. Triglycerides stored by WAT are synthesized (lipogenesis) through the uptake of fatty acids and glycerol-3-phosphate (the product of glycolysis). In turn, the breakdown of triglycerides to free fatty acids and glycerol is the source of energy (lipolysis). There are various hormonal mechanisms regulating these processes (Kersten, 2001). Insulin is the most important hormone involved in these processes. It stimulates lipogenesis by increasing the uptake of glucose to adipocytes as well as activating lipogenic and glycolytic enzymes. Additionally, insulin may inhibit hormone-specific lipase. Insulin sensitivity can be decreased by the effects of growth hormone that reduces lipogenesis. Lipogenesis is also inhibited by leptin that decreases food intake, stimulates the release of glycerol from adipocytes and increases oxidation of fatty acids. Moreover, leptin down-regulates expression of genes involved in lipogenesis and decreases the release of insulin (the adipoinvasive axis) (Kieffer and Habener, 2000). Other hormones that regulate these processes include sex hormones and glucocorticoids. Estradiol and testosterone have been shown to increase lipolysis (Mølgaard Hansen et al., 1980). In turn, the effects of glucocorticoids on lipogenesis and lipolysis differ in various physiological states (Wang et al., 2012). During fasting and starvation, increased levels of glucocorticoids stimulate lipolysis. However, chronically elevated levels of glucocorticoids contribute to enhanced lipogenesis and down-regulation of lipolysis. Importantly, WAT is an active organ secreting various hormones and other bioactive peptides that include, i.e., adiponectin, leptin, resistin, visfatin, interleukin(IL)-6, tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor-1 (PAI-1), angiotensin, sex hormones and glucocorticoids (Coelho et al., 2013; Guerre-Millo, 2002). Physiological role of hormones released by WAT and their role in the pathophysiology of schizophrenia were presented in subsequent sections.

There are several characteristics of BAT that allow to differentiate it from WAT. As opposed to WAT, adipocytes from BAT contain multiple lipid droplets and mitochondria (Cannon and Nedergaard, 2004). This type of adipose tissue is densely innervated by the sympathetic nervous system and has extensive vascularization (Betz and Enerbäck, 2015). The main BAT depot is located within the interscapular region and other depots are present along the great vessels and in the retroperitoneum (Betz and Enerbäck, 2015). BAT plays a unique thermogenic role due to the abundance of mitochondria that express the uncoupling protein 1 (UCP1) involved in adaptive thermogenesis.

Little is known about the composition of adipose tissue before the initiation of antipsychotic treatment. On the basis of a meta-analysis, it has been found that patients with FEP might present with higher levels of visceral adiposity (Shah et al., 2019). In turn, antipsychotics have been shown to profoundly impact biological processes within BAT. For instance, hyperphagia, weight gain and decreased locomotor activity during the treatment with risperidone have been associated with hyperthermia and increased expression of UCP1 in BAT as well as UCP3 in gastrocnemius from mice (Cope et al., 2009; Li et al., 2013; Singh et al., 2019). On the contrary, administration of olanzapine has been related to decreased percentage of brown adipocytes as well as reduced expression of UCP-1, proopiomelanocortin (POMC) and peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) in BAT from rats (Lian et al., 2014; Zhang et al., 2014a, 2014b). Interestingly, N-desmethyl-olanzapine, representing one of major olanzapine metabolites, has been found to induce the loss of body weight and fat mass in obese mice (Zhang et al., 2019a). These effects were accompanied by morphological changes in WAT, reduced production of IL-1β and increased expression of UCP1.

3. Adipose tissue hormones in schizophrenia and early psychosis

As mentioned above, WAT is now perceived as an endocrine organ that can produce a number of peptides involved in the regulation of appetite (see Fig. 1 for overview of main appetite regulating hormones). In this section, the role of WAT hormones that have extensively been studied in the pathophysiology of schizophrenia and weight gain induced by SGAs was discussed. These include adiponectin, leptin,
Adiponectin is a hormone released by WAT that regulates a number of metabolic processes related to glucose homeostasis, insulin sensitivity and oxidation of fatty acids (Wang and Scherer, 2016). It increases appetite and reduces energy expenditure by stimulating AMPK signaling in the hypothalamus (Kadowaki et al., 2008). In obesity, the levels of adiponectin remain elevated during food intake (Steinberg and Kemp, 2007). It has structural resemblance to TNF-α and the C1q complement protein. There are at least two forms of adiponectin – low molecular weight (LMW) adiponectin and high molecular weight (HMW) adiponectin. It has been suggested that only HMW adiponectin exerts biological activity. Reduced levels of adiponectin have been reported in obesity, diabetes and cardiovascular disease (Achari and Jain, 2017). Adiponectin improves insulin sensitivity, exerts anti-angiogenic and anti-atherogenic effects as well as down-regulates cell proliferation (Lihn et al., 2005). It stimulates β-oxidation in skeletal muscles and decreases lipid accumulation in the liver (Yamauchi et al., 2001). Some isoforms of adiponectin can cross the blood-brain barrier and interact with receptors in the hypothalamus, brainstem and cerebral cortex (Thundyil et al., 2012). However, the exact mechanisms linking adiponectin and schizophrenia pathophysiology remain unclear. It has recently been shown that infusion of adiponectin into the ventral tegmental area decreases basal activity and firing rate of dopaminergic neurons (Sun et al., 2019).

Meta-analyses of adiponectin levels have not provided evidence of altered adiponectin levels in drug-naïve patients with schizophrenia, including those with FEP (Bartoli et al., 2015b; Misiak et al., 2019). However, lower adiponectin levels have been found in patients with schizophrenia receiving SGAs. This association has been reported for clozapine and olanzapine but not quetiapine and risperidone (Bartoli et al., 2015a, 2015b). One of potential mechanisms underlying these observations might be related to weight gain induced by SGAs. However, there are some studies showing that lower adiponectin levels in medicated schizophrenia patients cannot be attributed to the effects of overweight or obesity (Sapra et al., 2016; Vedal et al., 2019). A recent study by Oh et al. (2012) also demonstrated that clozapine, but not quetiapine and ziprasidone, down-regulates expression of adiponectin gene in the mouse BAT. This effect was not observed in the study by Sarsenbayeva et al. (2019), who investigated the association between administration of olanzapine and expression of adiponectin in human subcutaneous adipocytes. It has also been found that antipsychotic treatment may disrupt the physiological association between liver fat and adiponectin levels but has no effect on the relationship between visceral and subcutaneous fat content with adiponectin levels in schizophrenia patients (Kim et al., 2017).

3.2. Leptin

Leptin is a hormone predominantly produced by WAT and enterocytes that regulates energy balance. It is able to pass through the blood-brain barrier and interacts with receptors expressed by neurons of the hypothalamus, cerebral cortex, hippocampus, basal ganglia and cerebellum (Farr et al., 2015). Effects of leptin on food intake are mediated by its interactions with receptors expressed by the arcuate nucleus of the hypothalamus. It decreases hunger by inhibiting the effects of neuropeptide Y and anandamide as well as stimulates satiety by increasing secretion of α-melanocyte-stimulating hormone (α-MSH). Importantly, it can also down-regulate lipogenesis by inhibiting the release of insulin (the adipoinisular axis) (Kieffer and Habener, 2000). It is of great importance that leptin-deficient not only develop obesity and related characteristics but also manifest reduced cortical volumes (Bereiter and Jeanraud, 1979; Farr et al., 2015; Vannucci et al., 1997). High leptin levels accompanied by leptin resistance are widely observed among obese individuals (Myers et al., 2010).

There is evidence that leptin may interact with dopaminergic neurotransmission. Desensitization of leptin receptors has been associated with up-regulation of dopaminergic genes in the prefrontal cortex (Del Rio et al., 2016). Moreover, leptin may also reduce dopaminergic outbursts in the mesolimbic system (Hommel et al., 2006). Animal models also support the role of leptin in the pathophysiology of schizophrenia. It has been shown that leptin increases prepulse inhibition in socially-isolated rats, suggesting its antipsychotic activity (Dashti et al., 2013). Impaired prepulse inhibition due to increased mesolimbic dopaminergic activity is now believed to represent one of schizophrenia-related phenotypes in animal models (Powell et al., 2009). Furthermore, there is evidence that leptin decreases basal and feeding-evoked release of dopamine in the rat nucleus accumbens (Krügel et al., 2003).

Several studies have also investigated the levels of leptin in patients with schizophrenia. Our group has recently performed a systematic review and meta-analysis of studies measuring the levels of leptin in FEP patients (Misiak et al., 2019). We found decreased leptin levels and increased insulin levels in antipsychotic-naïve patients with FEP. These findings might suggest that early psychosis is related to impairment of adipoinisular axis (Kieffer and Habener, 2000). On the contrary, another meta-analysis demonstrated elevated leptin levels in multi-episode schizophrenia patients, especially those receiving SGAs (Stubbs et al., 2016). Similar observations were reported by Potvin et al. (2015), who demonstrated that olanzapine, quetiapine and clozapine contribute to increased levels of leptin, whereas treatment with haloperidol and risperidone was associated with non-significant changes of leptin levels. Although changes in body mass and increased adiposity definitely account for changes of leptin levels observed by these studies, direct effects of antipsychotics on adipose tissue should also be taken into consideration. Horska et al. (2016) reported that olanzapine-depot administration induces weight gain in the absence of hyperphagia in rats and this effect appears to be accompanied by increased leptin levels in the initial phase of treatment. Moreover, it has been found that aripiprazole, clozapine and quetiapine induce expression of genes encoding adiponectin and leptin in human adipocytes in vitro (Sárvári et al., 2014). However, another study provided opposite findings by showing that clozapine and quetiapine down-regulate expression of leptin and/or adiponectin genes in BAT from mice (Oh et al., 2012). Finally, negative findings of studies in this field should also be acknowledged (Minet-Ringuet et al., 2007; Sarsenbayeva et al., 2019; Victoriano et al., 2010).
3.3. Resistin

Resistin is a bioactive peptide that is mainly produced by WAT; however, expression of the resistin gene has also been confirmed in the hypothalamus. It has been found that resistin exerts anorexigenic activity by decreasing expression of AgRP and NPY (orexigenic peptides) as well as increasing expression of cocaine and amphetamine-regulated transcript (CART) that is an anorexigenic peptide (Vázquez et al., 2008). On the other site, resistin decreases insulin sensitivity, stimulates pro-inflammatory response and oxidative stress, enhances lipogenesis as well as contributes to endothelial dysfunction (Acquarone et al., 2019). It has been found that resistin levels are elevated in patients with obesity and cardiovascular disease (Steppan et al., 2001). However, a potential cross-talk between resistin signaling and the pathophysiology of schizophrenia remains unknown. It has been reported that resistin may decrease the release of dopamine and norepinephrine in the hypothalamus (Brunetti et al., 2004).

Evidence regarding resistin levels in patients with schizophrenia is also largely limited. A recent meta-analysis of appetite regulating hormones in FEP revealed unaltered resistin levels in this group of patients (Misiak et al., 2019). However, this subgroup analysis was based on two studies (Bocchio-Chiavetto et al., 2018; Kriisa et al., 2017). The most recent study in this field (not included in this meta-analysis) demonstrated elevated levels of resistin in FEP and chronic schizophrenia patients (Sahepolat et al., 2020). There is also evidence that resistin levels are significantly higher in smokers with schizophrenia compared to non-smoking patients and positively correlate with the levels of interleukin-1 receptor antagonist and C-reactive protein (Klemettiä et al., 2017). However, effects of antipsychotics on the levels of resistin remain largely unknown. It has been found that clozapine may decrease the expression of resistin in brown adipocytes (Oh et al., 2012). However, observational studies of patients with FEP did not reveal any significant changes in the levels of resistin (Balodis et al., 2019; Perez-Iglesias et al., 2008).

3.4. Visfatin

Visfatin is produced by adipocytes and macrophages, and exerts multiple biological activities (Romacho et al., 2013). It is a potent activator of pro-inflammatory responses and this effect may also mediate its anorexigenic properties. There is also evidence that visfatin decreases food intake via stimulating proopiomelanocortin neurons and the activation of microglia (Tu et al., 2017). Visfatin has the nicotinamide phosphoribosyltransferase (NAMPT) enzymatic activity that accounts for the synthesis of nicotinamide adenine dinucleotide (Sommer et al., 2008). The NAMPT activity underlies its role in stimulating growth of vascular smooth muscle cells and angiogenesis (Peiró et al., 2010). Moreover, visfatin increases the synthesis of nitric oxide (Andrieieva et al., 2017). These activities may support the role of visfatin in the development of cardiovascular disease. Finally, visfatin can impact insulin sensitivity. Some studies have found that visfatin increases insulin sensitivity (Stokova, 2010), whereas other studies indicate that it may inhibit insulin signaling (Heo et al., 2019).

The role of visfatin in the pathophysiology of schizophrenia is yet to be established. Brunetti et al. (2012) found that visfatin treatment is associated with decrease of dopamine steady state levels in the hypothalamus in rats. A recent meta-analysis of appetite-regulating hormones revealed no significant differences in the levels of visfatin between FEP patients and healthy controls (Misiak et al., 2019). However, this observation was based on two studies (Basoglu et al., 2010; Bocchio-Chiavetto et al., 2018). Effects of antipsychotics on the levels of visfatin were investigated by two observational studies of FEP patients who had been drug-naïve at baseline (Basoglu et al., 2010; Perez-Iglesias et al., 2008). None of these studies reported significant changes in visfatin levels during antipsychotic treatment.

4. The hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis represents one of main biological systems involved in responses to stress and regulation of various metabolic processes. In brief, the activation of the HPA axis manifests in the production of the corticotrophin-releasing hormone (CRH) by the paraventricular nucleus. Subsequently, CRH triggers synthesis of the adrenocorticotropic hormone (ACTH) in the pituitary gland. The ACTH is produced by the cleavage of proopiomelanocortin (POMC) that is also expressed by peripheral tissues. In turn, ACTH stimulates the release of glucocorticoids, represented by cortisol, from the adrenal cortex. Finally, cortisol provides a negative feedback to the hypothalamus and pituitary gland leading to suppression of its own synthesis. Secretion of cortisol follows a circadian pattern with the highest levels of cortisol in the early morning and the lowest synthesis at midnight. Increase of the morning levels of cortisol has been named as the cortisol awakening response (CAR). Effects of the HPA axis response on feeding behaviors largely depend on a pattern of its activation. Acute stressors decrease food intake by stimulating the release of CRH that down-regulates neuropeptide Y (NPY) signaling (Reichmann and Holzer, 2016). Moreover, peptides released by the cleavage of POMC, including ACTH, melano-cyte stimulating hormone (MSH) and β-lipotropin represent anorexigenic signals. In turn, the release of glucocorticoids occurs with a delay and then stimulates feeding (Spencer and Tilbrook, 2011). It has been shown that cortisol increases the rewarding value of food through increasing the levels of insulin, leptin and NPY (Adam and Eppel, 2007). Therefore, prolonged exposure to stress may stimulate feeding and the development of obesity.

According to the neural diathesis-stress model, the HPA axis plays a central role in the onset and subsequent relapses of schizophrenia (Walker and Diforio, 1997). To date, numerous alterations related to dysregulation of the HPA axis have been reported in patients with schizophrenia and FEP as well as individuals at clinically high risk of psychosis. These include: 1) pituitary enlargement in individuals with prodromal symptoms who develop psychosis (Nordholm et al., 2013; Saunders et al., 2019); 2) blunted CAR and cortisol response to stress in patients with schizophrenia and FEP (Berger et al., 2016; Ciufolini et al., 2014; Zorn et al., 2017) and 3) increased blood cortisol levels in patients with schizophrenia and FEP (Girshkin et al., 2014; Hubbard and Miller, 2019). Higher plasma cortisol levels have been associated with increased visceral adiposity in drug-naïve FEP patients (Thakore et al., 2002). Moreover, it has been demonstrated that higher salivary cortisol levels are related to increased intake of saturated fat in subjects at risk of psychosis (Manzanares et al., 2014).

Antipsychotics may also impact the HPA axis through various mechanisms (Bradley and Dinan, 2010). Firstly, they can reduce a severity of various psychopathological symptoms, and thereby also cortisol levels. Secondly, antipsychotics may reduce the levels of ACTH and cortisol by direct pharmacological activity. However, there is some evidence that second-generation antipsychotics exert more potent activity with respect to the HPA axis than first-generation drugs. There are also studies showing that olanzapine and risperidone down-regulate expression of POMC, while risperidone might exert opposite effects (Ferro et al., 2011; Kursungoz et al., 2015; Sezlev-Bilecen et al., 2016).

5. The role of other hormones involved in the regulation of appetite in the pathophysiology of schizophrenia and early psychosis

5.1. Agouti-related protein and neuropeptide Y

The Agouti-related protein (AgRP) and neuropeptide Y (NPY) are orexigenic peptides produced by the same populations of neurons within the hypothalamus and the adrenal gland (Ilnytska and Argyropoulos, 2008). Additionally, other main sources of NPY production include the locus coeruleus, the solitary tract nucleus and the
septohippocampal nucleus (Reichmann and Holzer, 2016). There is a concordant pattern of central and peripheral release of AgRP. This peptide exerts biological activity via interactions with melanocortin receptors 3 and 4 (MC3R and MC4R). There is also evidence that AgRP may activate the hypothalamus-pituitary-adrenal (HPA) axis (Xiao et al., 2003) and inhibit the hypothalamus-pituitary-thyroid axis (Fekete et al., 2002). Peripheral AgRP can also impact adipocytes by altering the expression of fatty acids synthase (Claycombe et al., 2000) and leptin (Ebihara et al., 1999). On the other side, leptin inhibits hypothalamic expression of AgRP (Morrison et al., 2005). The levels of AgRP appear to be elevated in obesity and related conditions (Ilnytska and Argyropoulos, 2008). In turn, NPY stimulates food intake via direct interactions with its receptors (Y1 and Y5 receptors), GABA and α5 receptors. Moreover, NPY may increase appetite through inhibiting α-MSH signaling (Kalra and Kalra, 2004). There is also evidence that various anorexigenic signals (insulin, pancreatic polypeptides, estrogens and leptin) and orexigenic peptides (e.g., ghrelin) operate through interactions with NPY signaling (Kalra and Kalra, 2004).

It has been demonstrated that both AgRP and NPY may be involved in the pathophysiology of psychotic disorders. Several lines of evidence also indicate that AgRP may modulate dopaminergic neurotransmission in the mesocorticolimbic and mesostriatal circuitries (Roseberry et al., 2015). Experimental disruption of the AgRP circuitry has been found to enhance the activity of dopaminergic neurons in the ventral tegmental area associated with increased dopamine levels in the basal forebrain (Dietrich et al., 2012). Potential involvement of NPY in the pathophysiology of psychosis has been shown by several studies. Indeed, there has been found that the knockout of Disc1 gene decreases the number of NPY neurons (Deng et al., 2017; Morosawa et al., 2017). However, studies investigating the effects of targeting NPY receptors have provided mixed findings. It has been reported that the Y2 receptor deficiency impairs sensorimotor gating (Karl et al., 2010a), while the Y1 receptor knockout alters acoustic startle response (Karl et al., 2010b). Contrary to these findings, Stadlbauer et al. (2013) demonstrated that administration of the Y2 receptor agonist leads to impairments of social interactions and prepulse inhibition deficiency. There is consistent evidence from post mortem studies that patients with schizophrenia show reduced NPY expression in the prefrontal cortex (Cabrero and Hurd, 1999; Hashimoto et al., 2008; Kuromitsu et al., 2001; Mellios et al., 2009). Marginally decreased number of NPY neurons has also been found in the cortical nuclei of amygdala (Pantazopoulos et al., 2017). Finally, it has been found that NPY may activate the HPA axis (Inoue et al., 1999; Kakui and Kitamura, 2007). In contrast to these findings, NPY has been shown to exert anxiolytic and anti-stress effects (Heilig, 2004). Moreover, NPY regulates various biological processes that fall beyond food intake and include energy homeostasis, stress response, pain perception, circadian rhythms and cognition (Tatemoto, 2004).

Results of studies comparing the levels of AgRP in patients with early psychosis and healthy controls have not been published so far. One study reported no significant differences in the levels of AgRP between patients with schizophrenia receiving clozapine monotherapy and healthy controls (Wysokiński, 2015). Other studies have provided mixed findings. It has been reported that administration of olanzapine up-regulates expression of AgRP in the arcuate nucleus of the hypothalamus in rats (Kursungoz et al., 2015). Similarly, no significant changes in the levels of AgRP were found in a 3-month observational study of patients with schizophrenia receiving either ziprasidone or olanzapine (Ehrlich et al., 2012). These findings do not preclude the role of central AgRP signaling in antipsychotic-induced weight-gain. However, studies in this field have provided mixed findings. It has been reported that administration of olanzapine up-regulates expression of AgRP in the arcuate nucleus of the hypothalamus in rats (Fernø et al., 2011). Another study demonstrated opposite findings – lower hypothalamic expression of AgRP after administration of olanzapine in rats (Sezlev-Bilecen et al., 2016). Similarly, administration of risperidone has been shown to down-regulate expression of AgRP in the hypothalamus and peripheral blood (Kursungoz et al., 2015). In turn, unaltered levels of NPY have been demonstrated in the cerebrospinal fluid (CSF) of drug-free schizophrenia patients (Wideröv et al., 1988). However, higher CSF levels of NPY have been associated with worse functional outcomes (Stålberg et al., 2014). Interestingly, one study showed decreased expression of the Y1 receptor in the peripheral blood lymphocytes of schizophrenia patients (Vawter et al., 2004).

The potential role of NPY in SGAs-induced weight gain has extensively been studied. More specifically, weight gain induced by olanzapine has been associated with increase in the expression of NPY gene in the hypothalamus (Fernø et al., 2011; Weston-Green et al., 2012a). However, this effect was not observed after administration of risperidone (Kursungoz et al., 2015). It has been proposed that NPY alterations that appear during treatment with SGAs might be a target for novel interventions aimed at reducing metabolic adverse effects. There is evidence that administration of betahistine may reverse olanzapine-induced weight gain through the effects on NPY signaling in rats (Lian et al., 2014). Clinical trials also suggest that betahistine add-on treatment might be beneficial in terms of ameliorating weight gain associated with SGAs (Barak et al., 2016; Kang et al., 2018; Smith et al., 2018). Less is known about the effects of SGAs on NPY levels from human studies. It has been reported that quetiapine may increase CSF levels of NPY and this observation has been associated with anti-depressant and anxiolytic effects (Nikisch et al., 2012). Significant negative correlations between peripheral blood NPY levels and the dosage of olanzapine (Raposo et al., 2011) and clozapine (Marguliskas et al., 2018) have been found. However, no significant differences in peripheral blood levels of NPY between patients with schizophrenia receiving clozapine monotherapy and healthy controls have been detected (Wysokiński, 2015).

5.2. Ghrelin

Ghrelin is a hormone produced by enteroendocrine cells, especially those located in the stomach, as well as the hypothalamus. It increases food intake through interactions with receptors in the anterior pituitary gland and the arcuate nucleus of the hypothalamus. These effects are mediated by the release of neuropeptide Y (NPY) and AgRP (Goto et al., 2006). However, obesity is associated with reduced ghrelin levels, likely due to the activity of insulin and leptin (Tschöp et al., 2001). Ghrelin also exerts other biological activities, such as stimulation of gastrointestinal motility, modulation of sleep, increase of reward-seeking behaviors, regulation of glucose homeostasis, decrease of BAT thermogenesis, modulation of stress and anxiety behaviors as well as improvement of cardiovascular functioning (Müller et al., 2015).

Importantly, ghrelin receptors may also heterodimerize with other G-protein coupled receptors that include dopamine D1 and D2 receptors (Hedegaard and Holst, 2020). Moreover, administration of ghrelin to the tegmental area stimulates locomotor activity and increases the levels of dopamine in the nucleus accumbens (Jerlag et al., 2007). Neuroimaging studies also suggest the involvement of ghrelin in the pathophysiology of schizophrenia. There is evidence that ghrelin signaling might be involved in neural processing of appetitive stimuli that is specific for patients with schizophrenia. Indeed, Lungu et al. (2013) found that cerebral responses to food cues in the thalamus, parahippocampus and middle frontal gyri appear in schizophrenia but not in healthy controls. Activation of the parahippocampal region positively correlated with ghrelin levels.

According to a recent meta-analysis, which was based on three studies (Basoglu et al., 2010; Boccio-Chiavetto et al., 2018; Garcia-Rizo et al., 2012), ghrelin levels are unaltered in antipsychotic-naïve or minimally medicated FEP patients (Misiak et al., 2019). Another meta-analysis demonstrated that the treatment with olanzapine decreases ghrelin levels (Goetz and Miller, 2019). However, these results are contradictory to those obtained by animal model studies. Horska et al. (2016) revealed that olanzapine-depot administration does not lead to significant changes in serum levels of ghrelin in rats. Other studies demonstrated that olanzapine administration leads to up-regulation of...
ghrelin signaling accompanied by hyperphagia and weight gain (Weston-Green et al., 2012b; Zhang et al., 2014b). These discrepancies might be explained by differences in short- and long-term effects of antipsychotics on ghrelin levels. Earlier systematic review of studies investigating the association between SGAs and ghrelin levels in patients with schizophrenia suggested that ghrelin levels decrease in the first few weeks of treatment and then they appear to be elevated (Sentissi et al., 2008). These findings would further imply that changes in ghrelin levels in patients with schizophrenia are secondary to the treatment with SGAs. Moreover, a 16-week observational study revealed that administration of olanzapine increases neural responses to appetitive stimuli in the premotor area, somatosensory cortices and the fusiform gyri to similar levels observed in healthy controls. These effects were positively associated with changes in the levels of ghrelin that decreased during the observation period (Stip et al., 2012). Another study revealed a positive correlation between ghrelin levels and volumes of the fusiform cortex, superior temporal gyrus and inferior frontal operculum in patients with schizophrenia receiving olanzapine (Letourneau et al., 2011).

5.3. Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is a product of posttranslational modifications of proglucagon, and is released by enteroeendocrine cells of the intestine and neurons from the nucleus of solitary tract. It stimulates insulin secretion, decreases release of glucagon and inhibits gastrointestinal motility contributing to decreased food intake (Holst, 2007). It has been found that GLP-1 may also exert neuroprotective effects and impact learning and memory processes (Yildirim Simsr et al., 2018). Exendin-4, which is a GLP-1 analog, has been shown to protect dopaminergic neurons by inhibiting the activation of microglia and decreasing expression of matrix metalloproteinase-3 in mice (Kim et al., 2009). Another study demonstrated that liraglutide, representing GLP-1 agonists, exerts antipsychotic-like effects in mice (Dixit et al., 2013).

To date, results of one study investigating the levels of GLP-1 in early psychosis were published (Bocchio-Chiavetto et al., 2018). The authors found significantly lower levels of GLP-1 in FEP patients compared to healthy controls. The levels of GLP-1 in multiple-episode schizophrenia patients have not been investigated so far. Similarly, little is known about the effects of antipsychotics on the levels of GLP-1. It has been reported that clozapine and quetiapine lead to impaired glucose tolerance and insulin resistance that are independent of obesity and can be attributed to GLP-1 deficiency (Smith et al., 2009). Importantly, GLP-1 receptor agonists, such as exenatide and liraglutide, are now approved for the treatment of obesity and diabetes, and there is a growing interest in their use as concomitant treatments to prevent weight gain induced by SGAs (Kouidrat and Amad, 2019). A recent meta-analysis of three trials revealed that GLP-1 receptor agonists are effective and well-tolerable treatments for antipsychotic-induced weight gain, especially in case of patients receiving clozapine or olanzapine (Siskind et al., 2019). It has been proposed that GLP-1 receptor agonists may also improve cognitive performance (Edbrup et al., 2012); however, studies in this field have not provided evidence supporting their use as pro-cognitive medications in schizophrenia (Ishay et al., 2017).

5.4. Insulin

Insulin is the main hormone that regulates glucose homeostasis. It can cross the blood-brain barrier and suppress food intake via interactions with hypothalamic receptors (Pliquett et al., 2006). There is also evidence that insulin may regulate food intake by improving functional connectivity between the prefrontal cortex, the hypothalamus and the hippocampus (Küllmann et al., 2017). Insulin might be involved in the pathophysiology of schizophrenia. It has been found that there is a cross-talk between dopamine and insulin signaling, manifesting in the following observations: 1) cellular effects of dopamine and insulin converge on downstream effectors that include Akt and GSK3 signaling pathways; 2) short-term antagonism of dopamine D2 receptors increases insulin secretion and 3) insulin increases dopamine reuptake acutely, while chronic administration of insulin decreases dopamine reuptake (Nash, 2017).

On the basis of meta-analysis, our group demonstrated that antipsychotic-naïve FEP patients present with elevated insulin levels (Misiak et al., 2019). Moreover, higher insulin levels were related to higher severity of negative symptoms. These results are consistent with those obtained by other meta-analyses, suggesting that this group of patients present with indices of insulin resistance (Greenhalgh et al., 2017; Perry et al., 2016; Pillinger et al., 2017a). Less is known about brain insulin resistance in early psychosis. Zhang et al. (2019b) found that the measures of peripheral insulin resistance are associated with white matter dysconnectivity and cognitive impairment in drug-naive FEP patients. Impaired insulin signaling has also been found in drug-naive FEP patients at the level of peripheral blood extracellular vesicles that are enriched for neuronal origin (Kapogiannis et al., 2019). Moreover, it has been shown that differential expression of dopaminergic genes in the dorsolateral prefrontal cortex and the hippocampus can be attributed to altered expression of insulin signaling genes in schizophrenia (Mansur et al., 2018). These findings are consistent with those showing that stimulation of insulin/insulin growth factor-1 receptors in the human neuroblastoma cells alters expression of genes encoding proteins involved in metabolic and synaptic functions in a manner reflecting alterations observed in schizophrenia (Altar et al., 2008).

Even single dose of SGAs can lead to profound alterations of insulin signaling and glucose metabolism and the liver appears to be the main target organ of these effects (Agarwal et al., 2019). However, it is now increasingly being recognized that impairment of central insulin signaling might also be relevant to weight gain induced by SGAs. For instance, Castellani et al. (2018) found that acute administration of olanzapine can completely abolish the propensity of intracerebroventricular administration of insulin to reduce food intake. Reduced number of neurons expressing insulin-degrading enzyme has been found in chronic schizophrenia patients receiving haloperidol (Bernstein et al., 2009). Moreover, reduction of the ventral diencephalon volume, of which hypothalamus is the main structure, has been associated with weight gain, increase in glucose levels and decrease in high-density lipoproteins following antipsychotic treatment in FEP patients (Emsley et al., 2015).

5.5. Orexins

Orexins A and B, also known as hypocretins, are neuropeptides with multiple biological activities that are mainly produced by perifornical neurons and lateral hypothalamus. They play a critical role in maintenance of wakefulness and arousal. Orexin neurons are regulated by the availability of glucose, leptin and ghrelin. Indeed, high concentrations of glucose and leptin lead to hyperpolarization of orexin neurons, while low levels of leptin and ghrelin tend to depolarize them (Chieffi et al., 2017). Increased activity of orexin A leads to increased food intake by reducing postigestive feedback inhibition (Baird et al., 2009). Moreover, orexin A has been shown to stimulate lipogenesis and modulate BAT thermogenesis (Perez-Leighton et al., 2014).

Several observations suggest that orexins might be involved in the pathophysiology of schizophrenia. Decreased connectivity between midline-intralaminar thalamic nuclei and the prefrontal cortex, which includes several orexin neurons, has been observed in FEP patients and associated with cognitive deficits (Lambe et al., 2007). However, no significant differences in the levels of orexin A were found between FEP patients and healthy controls (Bosoglu et al., 2010; Misiak et al., 2019; Sun et al., 2016).
It has been shown that the activation of orexin-1 receptors plays an important role in the effects of SGAs on dopaminergic neurons (Rasmussen et al., 2007). Activation of orexin neurons might account for the efficacy of SGAs and their propensity to induce weight gain (Fadel et al., 2002). Surprisingly, it has been that peripheral blood orexin A levels are increased in medicated schizophrenia patients, especially those receiving less obesogenic antipsychotics (Chen et al., 2018).

Consistent with these findings, Dalal et al. (2003) found lower CSF levels of orexin A in patients with schizophrenia receiving haloperidol. Similarly, Basoglu et al. (2010) revealed a decrease in orexin A levels after 6 weeks of olanzapine treatment. Chien et al. (2015) also found elevated orexin A levels in medicated patients with schizophrenia compared to controls. However, no significant differences in the levels of orexin A were found between patients receiving antipsychotics of various weight gain liabilities. Interestingly, patients with higher orexin A levels had a lower severity of negative and disorganization symptoms.

6. Appraisal of evidence and future directions

This review implies that certain alterations of appetite regulating hormones appear in FEP patients. These include low levels of leptin and GLP-1 together with elevated insulin levels (see Table 1 for a summary of main alterations). However, evidence of altered GLP-1 levels is based on one large study of FEP patients. Addressing alterations of GLP-1 levels in early psychosis and medicated schizophrenia patients might hold a great promise for implementing GLP-1 receptor agonists to daily practice and early intervention toward preventing cardiovascular comorbidity. This is of particular importance since results of first clinical trials investigating the efficacy of GLP-1 receptor agonists in alleviating weight gain induced by SGAs have already been published (Siskind et al., 2019). However, our understanding of the role of GLP-1 in the pathophysiology of psychosis is largely limited. Similarly, there is a great need to provide mechanistic insights into the adiposinsular axis dysregulation in early psychosis (lower leptin and higher insulin levels) as pharmacological interventions targeting leptin resistance are in development (Santoro et al., 2015). Understanding hormonal regulation of appetite in early psychosis would also benefit from more studies looking at the levels and biological activity of other hormones (AgRP, ghrelin, NPY, orexin A, resistin and visfatin) or novel molecules that are likely involved in the regulation of metabolic processes, e.g., nesfatin-1 (Stengel et al., 2013; Ünal et al., 2018). Furthermore, there is also a great need of longitudinal studies investigating hormonal regulation of appetite in subjects at risk of psychosis. Attribution of altered hormonal regulation of appetite to genetic backgrounds shared between schizophrenia and cardiometabolic diseases is not the only hypothesis needed to further be tested by future studies. Indeed, studies exploring the effects of environmental exposures and lifestyle characteristics acting in the premorbid phase of psychosis on hormonal regulation of appetite are also warranted. For instance, some data suggest that early-life stress might be relevant to altered hormonal regulation of appetite in psychosis. For instance, Tosato et al. (2020) found that a history of childhood trauma might be related to significantly higher levels of insulin and C-peptide in FEP patients. However, the authors found no significant association between a history of childhood trauma and the levels of other peptides (leptin, ghrelin, resistin, visfatin, GLP-1, glucagon, gastric-inhibitory peptide and plasminogen-activator-inhibitor-1).

Impairment of hormonal regulation of appetite may change and/or progress with illness duration. Patients with multiple-episode schizophrenia may present with elevated levels of insulin, leptin and orexin A together with decreased levels of adiponectin. In addition, patients receiving olanzapine may show low ghrelin levels. However, more studies investigating the impact of SGAs on ghrelin levels are needed to dissect short- and long-term effects. There is also consistent evidence from post mortem studies that reduced number of NPY neurons appears in patients with schizophrenia. Studies on medicated schizophrenia patients and animal model studies provide important insights into the mechanisms underlying the development of weight gain induced by SGAs. It is important to note that interactions with serotoninergic and histaminergic receptors are not the only mechanisms of SGAs’ action that contribute to metabolic adverse effects. There is evidence that SGAs may initiate profound changes in the hormonal activity of WAT and the central regulation of appetite that cannot simply be perceived as the consequence of weight gain. However, insight into the central regulation of appetite from human studies is limited. Therefore, applying advanced neuroimaging approaches investigating neural responses to food cues is needed.

The impact of other concomitant medications on hormonal regulation of appetite cannot be excluded. It has been shown that patients with schizophrenia are more likely to develop metabolic syndrome compared to patients with schizophrenia and other non-affective psychotic disorders (Bartoli et al., 2015c). It might be hypothesized that this difference is attributable to the effects of other concomitant medications, such as mood stabilizers or antidepressants. In addition, the impact of mood symptoms related to sedentary behaviors should be taken into consideration. At this point, it is important to note that metabolic dysregulations in multiple-episode schizophrenia patients are similar to those observed in patients with other mental disorders, including major depression (Hryhorczuk et al., 2013), bipolar disorder (McElroy and Keck, 2014) and post-traumatic stress disorder (Bartoli et al., 2020). However, little is known about metabolic abnormalities in medication-naive patients with these disorders.

In summary, impairment of hormonal regulation of appetite is one of important aspects of schizophrenia pathophysiology that occurs in early phases of illness. Current evidence regarding the efficacy of pharmacological and non-pharmacological interventions aimed at preventing or treating cardiometabolic diseases in people with schizophrenia is largely limited. Therefore, understanding specific mechanisms underlying comorbid physical health impairments may improve the development of specific treatment strategies.

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Declaration of Competing Interest

None to declare.
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