Review Article

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Can we run away from the metabolic side effects of antipsychotics?

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Abstract: Antipsychotic (AP) medications are used to treat schizophrenia and a number off-label conditions. Although effective in reducing psychoses these drugs increase the risk of developing cardiometabolic disease, and are one of the reasons why individuals with schizophrenia live ~15–20 years less than the general population. While weight gain has traditionally been thought to be the primary culprit linked to increases in rates of cardiometabolic disease, there are weight-gain independent effects of antipsychotics. The purpose of the current review was to highlight the acute metabolic complications of antipsychotics and to address the question: are exercise and targeting "exercise-activated" signaling pathways, a viable approach to offset the metabolic complications of APs? The possibility of fibroblast growth factor 21 being a common factor mediating the protective effects of exercise and certain nutritional approaches against the acute metabolic complications of antipsychotics was also discussed. The research highlighted in this narrative review provides evidence, in preclinical models, that exercise and certain exercise-activated pathways, can protect against acute perturbations in glucose metabolism. While promising, further work is needed to confirm these findings in clinical populations prescribed antipsychotics.

Keywords: antipsychotic; mouse; glucose; exercise; AMPK; FGF21

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Introduction

Antipsychotic (AP) medications are used in the management of schizophrenia, a disease which impacts ~1 % of the population [1]. Additionally, APs are increasingly used in the treatment of a number of off-label conditions including anxiety, dementia, attention deficit, bipolar, depressive and sleep disorders [2–5]. In large part due to offlabel use, the prescription of APs has increased dramatically with recent estimates suggesting ~60 % increase globally between 2014 and 2019 [6]. APs are reported to have serious metabolic side effects that impact ~70 % of individuals taking these drugs [7]. While long term treatment with APs lead to weight gain [8–10], there are also weight gain independent metabolic consequences [11–17] including dysregulated glucose metabolism that occurrs within hours of treatment [12–14]. These combined effects of APs are linked to an increased risk of developing type 2 diabetes [18] and cardiovascular disease [19]. Concerningly, individuals prescribed APs often display reductions in physical activity [20], obesity and impaired glucose homeostasis prior to treatment [21]. These factors, in combination with the metabolic complications of APs, are primary reasons why individuals with schizophrenia die ~15–20 years earlier than the general population [22].

Standard of care in preventing the metabolic consequences of APs is metformin [23], a drug which reduces weight gain and lowers blood glucose [24]. Unfortunately, <20 % of individuals administered APs lose significant weight with metformin [25]. As APs impact multiple organs, and have both short and long-term effects, the design of approaches to lessen the metabolic consequences of these drugs has proven challenging. Adherence to APs is poor and the development of metabolic side effects has been identified as a reason why [26, 27]. The discontinuation of treatment has negative impacts on mental health including relapse and increases in attempted suicide [26] and thus mitigating the metabolic complications of APs has relevance to both the physical and mental well-being of individuals taking these drugs. Within this context, the overall goal of this narrative review is to answer the question: are exercise and targeting "exercise-activated" signaling pathways a viable approach to

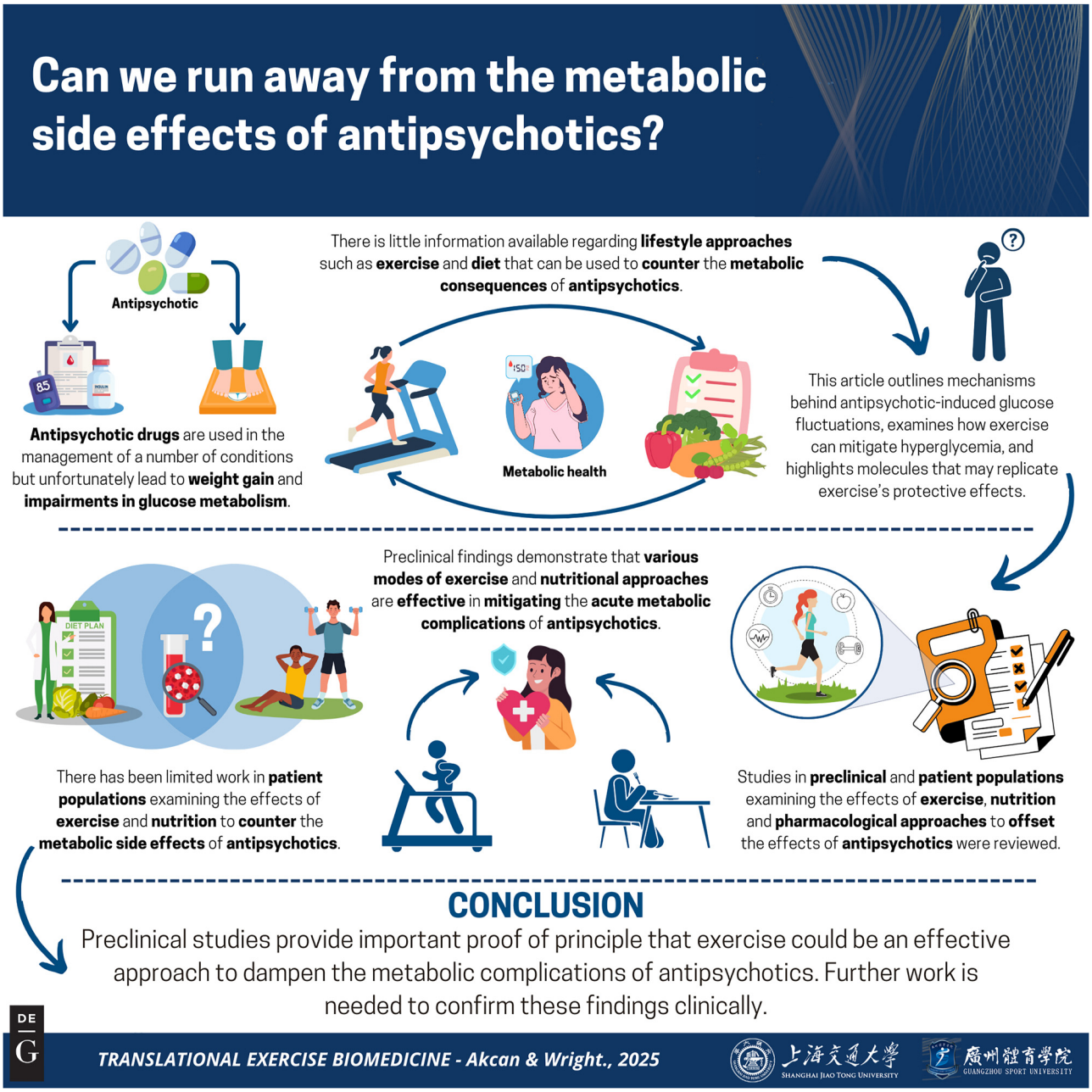

Figure 1: Graphical representation of this study. Key points: (1) antipsychotics are used in the management of schizophrenia and an increasing number of off label conditions. (2) They have negative metabolic side effects including weight gain and causing transient spikes in blood glucose. (3) Preclinical findings demonstrate that exercise and diet can protect against the metabolic side effects of antipyschotics. Figure created with BioRender.

offset the metabolic complications of APs? We will first provide a brief overview of the potential mechanisms driving AP-induced fluctuations in blood glucose, we will then discuss the utility of various modes of exercise in protecting against AP-induced hyperglycemia and finally examine the potential of several molecules that are increased or activated with exercise, that might be able to recapitulate the protective effects of this intervention. The summary of this article is presented in Figure 1.

Content

Acute, weight gain independent effects of APs on glucose and lipid metabolism

First generation, or typical APs were first used in the 1950's to treat psychosis. While the metabolic consequences of earlier iterations of APs were generally not as severe as current

pharmacotherapy options for severe mental illness, and in fact, in some cases have been shown to possess beneficial metabolic effects [28, 29], these drugs are no longer widely prescribed due to the development of movement disorders. Second generation APs antagonize dopamine, serotonin, histamine and muscarinic receptors [30] and are now used in the management of schizophrenia, major depressive and bipolar disorders, amongst others [31]. Olanzapine, risperidone and quetiapine are among the most widely prescribed APs [4], with olanzapine and clozapine, an AP used in the management of treatment refractory schizophrenia, having the greatest metabolic liability [32]. Concerningly even APs considered to be more metabolically neutral (such as aripiprazole) they are still associated with significant weight gain in AP naïve individuals; and APs, regardless of class, confer approximately a 2–4-fold increased risk above schizophrenia alone for development of type 2 diabetes [33].

While AP-induced perturbations in glucose metabolism were initially thought to be due to weight gain, direct effects have been reported [11–17]. In healthy individuals, acute treatment with APs, in the absence of weight gain, causes impaired glucose tolerance [11] and insulin resistance [17] within hours after treatment [12]. Acute effects of APs on glucose metabolism are also seen in rodents where APs cause rapid hyperglycemia [13, 14], an effect that does not dissipate with prolonged use [34] and is exaggerated in conditions of pre-existing metabolic dysfunction [35]. Interestingly, these effects, at least in mice, appear to be sex specific, with females not displaying increases in blood glucose following AP treatment [36]. Repeated hyperglycemic episodes, as could occur following each dose of AP, are harmful and could increase the risk for the development of cardio-metabolic disease. For example, transient blood glucose excursions can be more harmful than chronically elevated blood glucose in reducing endothelial function and increasing oxidative stress [37, 38], factors implicated in the cardiovascular complications of diabetes [39]. Thus, it is important to identify mechanisms driving increases in blood glucose with APs and identify approaches to mitigate these effects.

In preclinical models, acute treatment with APs leads to insulin resistance in skeletal muscle, adipose tissue and liver [35], reductions in insulin secretion [40] and increases in liver glucose production [13, 41]. Excursions in blood glucose with APs are paralleled by indices of sympathetic outflow including increased concentrations of glucagon [36, 42–44] and catecholamines [45, 46], neuroendocrine signals that stimulate liver glucose production [47]. Glucagon is a crucial signal mediating AP-induced impairments in glucose metabolism. We have found that AP-induced hyperglycemia and markers of liver glucose production are absent in mice lacking the glucagon receptor [48]. Similarly, female mice who do not develop hyperglycemia following acute treatment with APs, also do not display increases in serum glucagon following treatment [36].

APs also acutely perturb lipid metabolism as shown by rapid increases in whole body fat oxidation [14, 36, 42], an effect thought to be a compensatory response to reductions in glucose utilization [14]. While not a universal finding [14], we found that acute AP treatment increases indices of adipose tissue lipolysis in mice in the fed state [36, 42]. This effect might be mediated by AP-induced increases in catecholamines [45, 46], stimulators of adipose tissue lipolysis [49], and/or reductions in the ability of insulin to suppress lipolysis. Fatty acids could be linked to AP-induced hyperglycemia as adipose derived metabolites are a source of gluconeogenic substrate for liver glucose production [50]. The mechanisms driving AP-induced increases in lipid utilization and how this could be linked to perturbed glucose metabolism are areas requiring further exploration.

Approaches to mitigate AP-induced metabolic dysfunction

Standard of care in treating the metabolic complications of APs is metformin [23], a widely prescribed glucose lowering agent which also causes weight loss. Though inexpensive, <20 % of individuals taking APs lose appreciable weight with metformin [25]. Although metformin does protect against acute AP-induced liver insulin resistance, it does not protect against peripheral insulin resistance [41]. Recent work [51], including data from our group [42], has highlighted the utility of glucagon like peptide 1 (GLP-1) receptor agonists in protecting against AP-induced hyperglycemia. However, given limited insurance coverage and accessibility issues these drugs have not been widely incorporated into the clinical management of AP-induced metabolic dysfunction. Another potential barrier to treatment is that GLP1 receptor agonists are typically administred by subcutaneous injection, and a pilot study found that fewer than half of patients with schizophrenia reported being comfortable self-administering injections [52]. Given these issues our goal has been to identify new targets to dampen the metabolic complications of APs.

Exercise

Exercise has profound effects on glucose homeostasis with a single bout of exercise increasing insulin-independent muscle glucose uptake during and for several hours post exercise [53]. As increases in contraction stimulated skeletal

muscle glucose uptake subside, muscle develops an enhanced sensitivity to insulin [54] which can last for a prolonged period of time depending upon the duration and intensity of exercise that was performed. Within this framwork we reasoned that AP-induced increases in blood glucose would be blunted in mice that had previously exercised. We found that a single session of exhaustive (20° incline, initial speed 12 m/min and increased 1 m/min every 10 min, ~75 min in total) but not moderate intensity (~75 % VO_2 max, 75 min) treadmill running immediately before treatment protected against olanzapine induced increases in blood glucose in mice [55]. While these results are promising, the prescription of exhaustive exercise to those being treated with APs is not realistic, as they are a patient population who already exhibit poor adherence to exercise treatment. Given this we repeated these experiments using voluntary wheel running. This approach has several advantages compared to forced treadmill exercise including the pattern of physical activity being similar to the natural running behavior of the animal and the removal of stress due to animals being handled [56]. Similar to what was found with forced treadmill running, olanzapine induced hyperglycemia was attenuated in mice given access to a voluntary running wheel (~5 km of running) the previous night [43]. These protective effects persisted for upwards of 7 h after exercise and were maintained in mice with diet induced obesity, a model which displays an exaggerated increase in the acute blood glucose response to olanzapine [35]. From a mechanistic perspective, protection against hyperglycemia was mirrored by attenuated increases in circulating glucagon and slight improvements in whole body insulin tolerance [35].

Interleukin 6

Forced treadmill and voluntary wheel running provide important proof of principle, in a preclinical model, that exercise can be an effective tool to dampen the excursions in blood glucose that occur following treatment with APs. With this said, the implementation of "lifestyle approaches" would likely be difficult given poor adherence in individuals taking APs [57, 58]. Given this we have been using exercise as an approach to identify potential mechanisms that could be targeted dampen the acute metabolic complications of APs. Our initial studies using forced treadmill running identified a clear intensity dependent effect of exercise on protecting against the rise in blood glucose following treatment with olanzapine in mice. Exercise increases circulating levels of interleukin 6 (IL-6), a signaling molecule that has been postulated to play a role in the effects of exercise on substrate utilization [59]. As prior exhaustive, but not moderate, exercise protected against olanzapine induced hyperglycemia while at the same time increasing IL-6, we interrogated the potential role of IL-6 in protecting against AP-induced hyperglycemia. We found that acutely treating mice with recombinant IL-6, despite leading to supraphysiological circulating concentrations did not prevent increases in blood glucose with olanzapine treatment [55]. Moreover, the ability of exercise to protect against olanzapine induced hyperglycemia was maintained in IL-6 knockout mice and in mice treated with IL-6 neutralizing antibodies [55]. Collectively, these findings provide evidence that IL-6 is not sufficient nor necessary for the effects of exercise to protect against AP-induced perturbations in glucose homeostasis.

5'AMP activated protein kinase (AMPK)

As IL-6 did not appear to be either sufficient, or necessary for exercise, to dampen olanzapine induced hyperglycemia, we turned our attention to another molecule linked to the metabolic effects of exercise, AMPK. This enzyme is activated in conditions of energetic stress and has been shown to increase insulin-independent skeletal muscle glucose uptake [60], enhance skeletal muscle insulin sensitivity [61] and attenuate liver glucose production [62], processes that would be expected to counter AP-induced increases in blood glucose. As AMPK is activated by exercise in an intensity dependent manner, we interrogated if the pharmacological activation of this enzyme would protect against acute AP-induced increases in blood glucose. The first approach that used was to co-treat mice with 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), while being challenged with olanzapine. AICAR is an analog of adenosine that is taken up by tissues, phosphorylated and converted to 5-aminoimidazole-4-carboxamide ribonucleoside 5'-monophosphate (ZMP) [63]. Like increases in AMP, ZMP activates AMPK, though it should be noted that some of the effects of AICAR are likely AMPK-independent [63]. It was found that treatment with AICAR attenuated the rise in blood glucose, the development of insulin resistance and increases in indices of liver glucose production in mice treated with olanzapine [64].

AICAR has AMPK independent effects [63] and thus it is critical to determine if more specific AMPK agonists would have similar protective effects. In this regard A769962, a specific activator of AMPK β1 containing complexes [65], which are found primarily in the liver in mice [66], also attenuated olanzapine-induced increases in blood glucose, whereas the effects of olanzapine on blood glucose were potentiated in AMPK $\beta1^{-/-}$ mice [67]. These results are consistent with clinical findings highlighting associations between polymorphisms in AMPK subunits and AP-induced

weight gain [68]. To date the utility of using AMPK agonists to offset the metabolic complications of APs in clinical populations has not been addressed. With this being said, there have been several studies demonstrating beneficial effects of AMPK agonists on glucose metabolism in human participants [69, 70]. While promising caution is likely needed as treatment with certain AMPK agonists have been reported to cause cardiac hypertrophy in non-human primates [71]. An additional concern is that activation of AMPK in the hypothalamus has been linked to increases in liver glucose production [72], a process that is thought to be involved in mediating acute AP-induced increase in blood glucose [48]. If AMPK were to be targeted to offset the metabolic consequences of APs, then it would be important to design pharmacological agents that do not cross the blood-brain barrier.

An important, and as of yet, unresolved question is if AMPK is required for the protective effects of exercise against AP-induced perturbations glucose metabolism. The data to date would suggest that this is not the case, as the ability of voluntary wheel running to attenuate AP-induced increases in blood glucose were intact in AMPK $\beta1^{-/-}$ mice [43]. A caveat to these findings however is that an acute bout of voluntary wheel running (~3–5 km/night) might not be a sufficient stimulus to robustly activate AMPK. Moreover, since AMPK β1 containing complexes are primarily found in the liver in mice [66], and given that the protective effects of exercise could be mediated via alterations in cell types besides hepatocytes, then tissue specific AMPK knockout mice, i.e., muscle specific AMPK knockouts, need to be tested.

Fasting and ketogenic diets

In addition to exercise and exercise-activated pathways, there is accumulating evidence that nutritional manipulations can also dampen AP-induced increases in blood glucose. An unappreciated determinant of the acute metabolic response to APs is nutritional state. Ikegami and colleagues [73] measured the blood glucose response to acute olanzapine treatment in mice in the fed state, or following a 16 h fast. While not directly compared, the rise in blood glucose with olanzapine appeared to be markedly dampened in fasted mice [73]. To examine this in more detail we completed similar experiments and directly compared the blood glucose and endocrine response to olanzapine between fed and fasted mice. Similar to the initial work by Ikegami et al. [73] olanzapine-induced increases in blood glucose were blunted in fasted mice and this was paralleled by a reduced ability of olanzapine to increase circulating concentrations of glucagon [44].

Fasting is a robust perturbation that induces a wide range of metabolic adaptations to ensure the adequate provision of fuel. One of the hallmark features of fasting are increases in whole body fatty acid oxidation and elevations in circulating concentrations of ketone bodies. Interestingly, several groups have shown that ketones, such as beta hydroxybutyrate (βHB) can reduce glucagon secretion from the pancreas [74–76]. Given this we examined if acutely increasing βHB through either injecting mice with the compound, or gavaging them with oral ketone esters, would recapitulate the effects of fasting. Surprisingly, this did not turn out to be the case leading us to postulate that more prolonged increases in circulating ketones might be necessary to protect against AP-induced hyperglycemia [44]. To test this, we fed mice a ketogenic diet for 2 days prior to an acute challenge with olanzapine, and similar to fasting, found that a ketogenic diet blunted the rise in blood glucose and serum glucagon. These findings provide evidence that prolonged increases in circulating ketone bodies are sufficient to protect against olanzapine induced hyperglycemia, and while associative and not causative, might suggest that this could be one potential mechanism through which fasting confers protection against acute AP-induced perturbations in glucose metabolism. Work in preclinical models would appear to have some degree of translational relevance as several studies have recently demonstrated improvements in metabolic and mental health in individuals with schizophrenia and bipolor disorder given ketogenic diets [77–79]. Like many restrictive diets, adherence to a ketogenic diet for a prolonged period of time could prove challenging, particularly in this patient population and thus it will be important to determine the feasibility of adjunctive treatment with ketogenic diets in individuals with severe mental illness.

Could there be a unifying factor mediating the protective effects of exercise, fasting and ketogenic diets?

A single session of exercise [43, 55], fasting [44] or a ketogenic diet [44], all dampen AP-induced hyperglycemia in mice (Figure 2). While these interventions pose unique metabolic challenges it is interesting to speculate if there could be a common, unifying factor, potentially explaining the protection against fluctuations in blood glucose following AP-treatment. One candidate molecule could be Fibroblast Growth Factor 21 (FGF21). FGF21 is increased with exercise [80, 81], fasting [82, 83] or the consumption of a ketogenic diet [84, 85]. FGF21 is highly expressed in the liver [86] and pancreas [87] and to a lesser extent in adipose tissue [88], and skeletal muscle [89]. FGF21 signals through a receptor complex consisting of FGF receptors (FGFR1c, FGFR2c, FGFR3c) and a co-receptor named β-Klotho. While FGF receptors are widely expressed, β-Klotho is restricted primarily to adipose, liver, pancreas and the brain [90, 91], and confers specificity for FGF21 signaling. Interestingly, β-Klotho, is expressed in

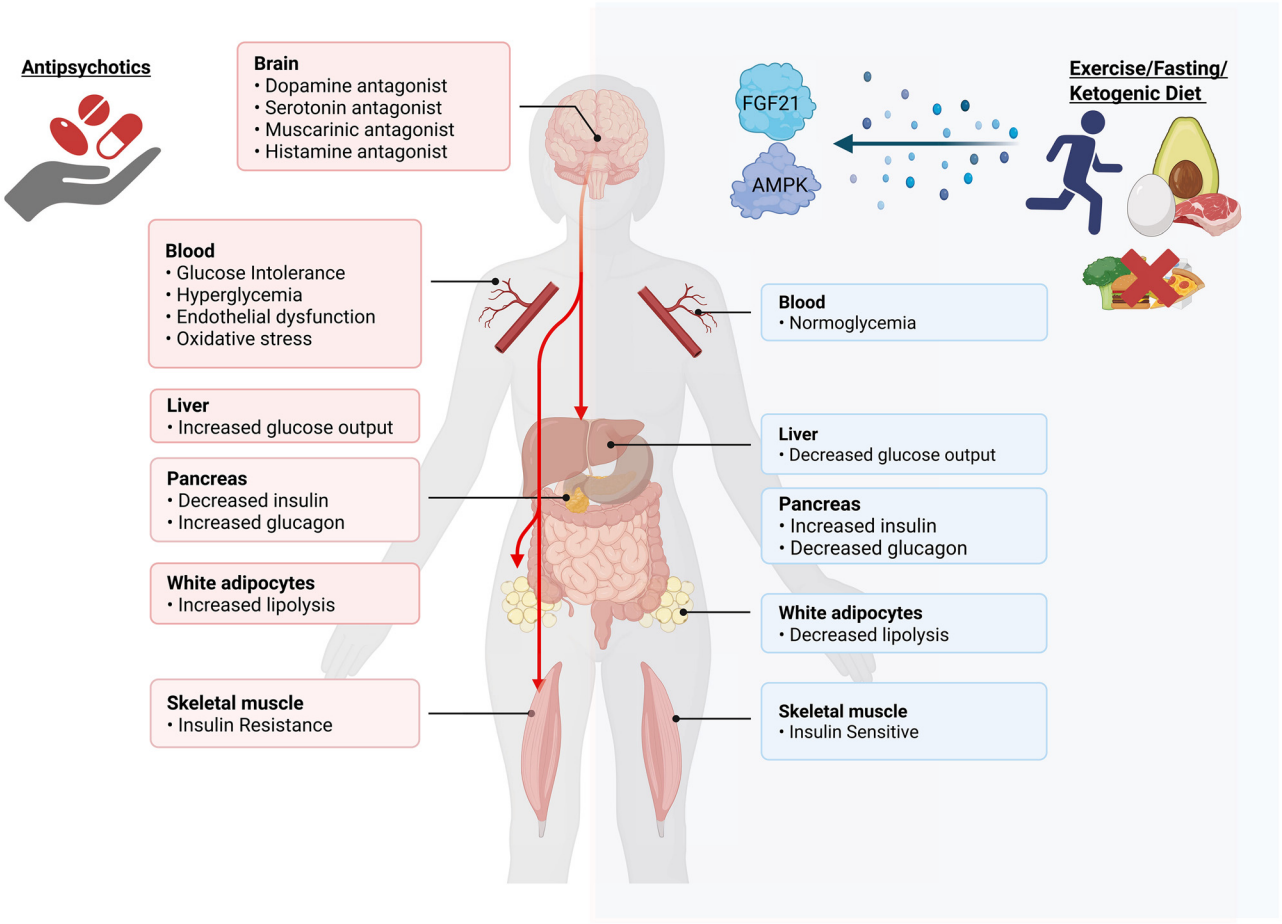

Figure 2: Schematic representation of the underlying mechansims of how acute treatment with antipsychotics increases blood glucose and how exercise, fasting and ketogenic diets can potentially protect against this.

many of the same tissues that are impacted by APs. For example, FGF21 reduces circulating glucagon [92, 93], a mediator of AP-induced increases in liver glucose production [48], and some [93], but not all [94], have shown that FGF21 directly attenuates glucagon secretion from cultured pancreatic islets. Additionally, treatment with FGF21 reduces liver glucose production and increases liver insulin action in mice [92, 94], processes perturbed with acute AP treatment [35, 36]. Fatty acids are an important substrate for liver glucose production [50], and it has been argued [95] that the glucose lowering effects of FGF21 are linked to decreases in lipolysis. While the potential of FGF21 to mitigate the metabolic consequences of APs has not been empirically tested, there is a strong rationale for exploring this possibility in further detail.

Summary and outlook

The goal of this review was to address the question if exercise, and targeting “exercise-activated”signaling pathways, is a viable approach to offset the metabolic complications of APs. The work highlighted in this review, though almost exclusively preclinical, provides evidence that this could be the case. While these initial, pre-clinical findings are promising, there are further considerations in regards to clinical translatability that need to be addressed before this question can be fully answered. First, the experiments described in this review utilized otherwise healthy rodents. Schizophrenia is associated with the presence of metabolic dysfunction and this often presents in AP-naïve patients [96–98]. In rodents this can be modelled using maternal gestational treatment with polyriboinosinic-polyribocytidilic acid (poly [I:C]), a synthetic analog of double stranded RNA that induces pre-natal immune activation and the development of a schizophrenia like condition in the offspring [99, 100]. Given the existence of pre-existing metabolic dysfunction in this model it will be important to determine if exercise, and other interventions discussed above, can protect against acute AP-induced perturbations in glucose metabolism. Somewhat related to this point it will be important to

determine if exercise, or other interventions described in this review, impact the pharmacokinetics of APs, and perhaps by extension, their ability to treat symptoms of severe mental illness. Preliminary findings demonstrate that serum concentrations of olanzapine are not different in fasted compared to fed mice and in mice provided a ketogenic compared to chow diet [44]. These cursory findings might suggest that protection against the metabolic consequences of APs is not occurring secondary to reductions in drug exposure, however this needs to be examined in further detail. Clearly, reductions in the metabolic complications of APs at the expense of attenuated drug effectiveness in managing the underlying mental illness would be contraindicated for patients. Lastly, tightly controlled clinical trials testing the efficacy of exercise and other lifestyle interventions, against both the acute and chronic metabolic complications of APs initiated at the onset of treatment, are needed.

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