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The Effect and Mechanisms of Risperidone and Voluntary Exercise Intervention on Hepatic Lipid Metabolism in Juvenile Female Rats

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Abstract

Risperidone is a commonly used antipsychotic drug in juveniles, but with serious metabolic side-effects. Previous evidence suggests that exercise mitigates risperidone-induced hypertriglyceridemia and adipose accumulation, yet the underlying hepatic mechanisms remain unclear. In this study, female juvenile rats were randomly assigned to four groups (n = 8/group): Vehicle + Sedentary, Risperidone (0.9 mg/kg, twice daily) + Sedentary, Vehicle + Exercise (3-hour voluntary access to a running wheel/day), and Risperidone + Exercise groups (n = 8/group). Following 4-week treatment, liver tissue was harvested for subsequent analyses. Risperidone increased hepatic expression of fatty acid synthase (FAS) and upstream stimulatory factor 1 (USF1), while exercise attenuated these changes and elevated the pAMPK/AMPK ratio, indicating suppressed lipogenesis. Risperidone also upregulated peroxisome proliferator-activated receptor γ (PPARγ) and CD36, promoting lipid uptake and storage; these effects were reversed by exercise, which additionally reduced FSP27 expression. Furthermore, exercise enhanced lipolytic and β-oxidative capacity, as evidenced by increased adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and restoration of peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) levels suppressed by risperidone. Collectively, risperidone promotes hepatic lipid accumulation by stimulating USF1/FAS-mediated lipogenesis and PPARγ/CD36-driven uptake while suppressing the PGC1α

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signaling pathway associated with β-oxidation. Voluntary exercise counteracts these alterations, thereby ameliorating risperidone-induced hepatic lipid dysregulation.

Keywords
Antipsychotic drug; exercise; metabolic side effect; lipid metabolism; juvenile

1. Introduction

Risperidone, one of the most commonly prescribed second-generation antipsychotics (SGAs), accounts for approximately 70% of antipsychotic prescriptions in juveniles under 14 years of age [1]. However, it is associated with significant metabolic side effects, including weight gain, insulin resistance, and dyslipidemia, which can lead to metabolic syndrome [2]. Vulnerable populations such as children, adolescents, and females are particularly susceptible to these adverse effects [3, 4]. A prospective study reported that more than half (53.8%) of pediatric patients receiving risperidone experienced at least one metabolic abnormality, with hyperlipidemia being the most common (34.6%) [5]. Additionally, female sex, considered both a risk factor and a predictive marker for SGA-induced weight gain, likely reflects increased vulnerability due to sex-specific physiological characteristics, such as a higher proportion of adipose tissue and the modulatory influence of gonadal hormones [6-8].

Voluntary exercise has been shown to improve lipid metabolism [9]. In our previous work, we found that voluntary exercise significantly attenuated risperidone-induced increases in plasma triglyceride levels and adipose tissue accumulation in juvenile rats [10]. However, the underlying mechanisms responsible for these protective effects remain incompletely understood.

The liver is essential in maintaining whole-body lipid homeostasis by regulating the synthesis, storage, modification, and transport of lipids. Hepatic *de novo* lipogenesis contributes to the storage and secretion of lipids from hepatocytes [11]. Insulin activates lipogenic transcription factors [sterol regulatory element binding transcription factor 1c (SREBP1c), liver X receptor (LXR), and upstream transcription factor 1 (USF1)] upregulate the expression of lipogenic enzymes [e.g., Fatty acid synthase (FAS), Acetyl-CoA carboxylase1 (ACC1) and Stearoyl-CoA desaturase (SCD1)], resulting in fatty acid synthesis [12]. Synthesized fatty acids are stored in the liver on the form of triglycerides and exported into the bloodstream in very-low-density lipoprotein (VLDL) particles. Additionally, fatty acids could be released from triglycerides through the catalysis of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), and then plasma fatty acids are taken up into the liver by fatty acid transport protein 2 (FATP2), caveolin-1 (CAV-1) and cluster of differentiation 36 (CD36). Moreover, peroxisome proliferator-activated receptor α (PPARα) and γ (PPARγ) also modulate fatty acid uptake, trafficking, catabolism, utilization, triglyceride synthesis, and lipid droplet formation [13, 14]. Further, the majority of the fatty acids in hepatocytes is translocated into the mitochondria and undergo β-oxidation [15]. Carnitine palmitoyltransferase 1A (CPT1A), a downstream target of PPARα and a rate-limiting enzyme for fatty acid β-oxidation, facilitating fatty acids entering the mitochondrial matrix [16]. Peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α) collaborates with PPARα to regulate the expression of fatty acid oxidation enzymes in mitochondria [17]. Imbalances between lipid synthesis and degradation leads to lipid metabolism disorders.

Treatment with SGAs has been reported to disrupt hepatic lipogenesis, lipolysis, fatty acids uptake, and β-oxidation [18, 19]. Meanwhile, exercise improves lipid homeostasis by reducing synthesis and transport of fatty acids triglyceride in both adipose tissue and liver [20, 21]. To date, no study has investigated the mechanisms through which exercise ameliorates lipid metabolism disorders induced by risperidone. Therefore, this study explored the possible mechanisms driving the effects of voluntary exercise in alleviating risperidone-induced lipid metabolic disorders in a juvenile female rat model.

2. Materials and Methods

2.1 Ethics Statement

All experimental procedures were approved by the Animal Ethics Committee, University of Wollongong, Australia (AE18/19) and adhered to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes [22].

2.2 Animal Housing and Treatment

Animal housing and treatment protocols were conducted as previously detailed [10]. Briefly, juvenile female Sprague-Dawley rats (postnatal day 22/23) were obtained from the Animal Resource Centre (Perth, Western Australia). This study focused exclusively on female rats as this sex is well known to be particularly vulnerable to antipsychotic-induced metabolic and endocrine disruptions [23-27]. Moreover, the reductions in physical activity associated with risperidone treatment reported in humans are reliably replicated in female rat models [24, 28, 29]. At postnatal day 26/27, they were housed individually in Techniplast GR1800 ventilated cage (Lane Cove West, NSW, Australia), and randomly allocated into (1) Vehicle + Sedentary (VS), (2) Risperidone + Sedentary (RS), (3) Vehicle + Exercise (VE), and (4) Risperidone + Exercise (RS) groups (n = 8/group). Risperidone (Risperdal, Janssen, Macquarie Park, NSW, Australia) was calculated based on rat body weight at a total dose of 1.8 mg/kg/day (0.9 mg/kg per dose, twice daily at 07:00 and 19:00) in 0.3 g cookie dough pellets from postnatal days 29/30 for a duration of 4 weeks. Risperdal tablets were separated from their coating, then pulverized using a mortar and pestle [26]. Each Risperdal tablet has a total weight of approximately 100 mg and contains 1 mg of active risperidone. The required dose of powdered risperidone was mixed with the dry cookie ingredients (15% gelatine, 9% milk powder, 38% corn flour and 38% sugar), and then water was then added immediately prior to administration. The control rats were given same amount of plain cookie dough pellets at the same time. The dosage was translated from the clinical dose based on body surface area in accordance with FDA guidelines [30, 31], and has been shown to be physiologically and behaviorally effective in juvenile rats [24, 32-34]. On postnatal day 57/58, following overnight fasting, the final dose of risperidone was administered orally using a 1 mL syringe, with the drug dissolved in approximately 0.2 mL of water to avoid the potential impact of cookie dough on plasma glucose and lipid levels.

Rats were allowed to voluntarily access running wheels equipped with revolution counters for 3 hours daily in a 4-week period (from postnatal days 29/30 to 56/57), with traveling distance recorded (Scurry Rat Running Wheel/Chamber, Lafayette Instrument, IN, USA). The voluntary exercise protocol (3 hours per day for 4 weeks) was based on prior evidence demonstrating that a five-day-a-week, three-hour voluntary exercise intervention significantly ameliorated olanzapine-

induced metabolic side effect in adult female rats [23]. Additionally, Goh and Ladiges reported that a regimen of 1 hour per day, five days per week for five months improved body composition in young adult mice [35]. Before commencing the exercise intervention, rats in the exercise groups underwent a 3-day acclimation period, during which they were placed in the running wheel cages for 10 minutes each day. To minimize the sedative impact of risperidone, rats receiving risperidone participated in the exercise intervention 4 hours post-drug administration, while rats treated with the vehicle underwent exercise 1 hour after receiving cookie pellets. During the exercise sessions, rats were housed in a separate exercise cage with access to water but without food and were returned to their home cages after the exercise. To standardize food availability conditions for the 3-hour voluntary exercise group, all sedentary rats had their home cage food hoppers removed for the same 3-hour period.

All rats were euthanized by decapitation following isoflurane anesthesia on postnatal day 57/58. Tissue samples (liver, inguinal, perirenal, periovary, and mesentery adipose tissue) were harvested and weighed immediately, and then frozen in liquid nitrogen and kept at -80°C. Blood was collected from the left ventricle into EDTA tube, and the plasma was separated by centrifuge (4°C, 3000 rpm, 10 min) then stored at -80°C until further use.

As previously reported, risperidone treatment significantly reduced physical activity over the 28-day intervention period (Average distance travelled: RE group, 1656.13 ± 359.03 m/day vs VE group, 2828.00 ± 416.24 m/day, $p < 0.05$) [10]. Voluntary exercise reduced risperidone-induced increases in adipose tissue [periovary index (VS: 0.89 ± 0.06, RS: 1.27 ± 0.12, VE: 0.75 ± 0.06, RE: 0.85 ± 0.13), perirenal index (VS: 0.84 ± 0.09, RS: 1.06 ± 0.10, VE: 0.63 ± 0.04, RE: 0.78 ± 0.10) and inguinal (VS: 1.15 ± 0.09, RS: 1.56 ± 0.08, VE: 1.01 ± 0.05, RE: 1.25 ± 0.11)], fasting plasma insulin (VS: 85.27 ± 6.35, RS: 201.16 ± 48.08, VE: 129.27 ± 19.37, RE: 113.67 ± 16.76 pmol/L), and plasma triglycerides (VS: 0.67 ± 0.09, RS: 1.22 ± 0.18, VE: 0.56 ± 0.06, RE: 0.71 ± 0.08 mM) [10].

2.3 Western Blots

Procedures of the liver lysate preparations and Western blot were conducted as reported previously [10]. In brief, aliquots containing 15 μg protein were added to electrophoresis on a precast polyacrylamide (4-20%) gel (Bio-Rad Laboratories, Gladesville, NSW, Australia). transferred the separated protein to a polyvinylidene difluoride (PVDF) membrane (Bio-Rad Laboratories, Gladesville, NSW, Australia). Following transferred the separated protein to a polyvinylidene difluoride membrane, it was blocked with 5% skim milk plus 0.1% Tween-20 in Tris-buffered saline for a subsequent overnight incubation at 4°C with following primary antibodies: anti-SREBP1 (1:500, #ab28481, Abcam, Cambridge, UK), anti-SCD1 (1:1000, #ab19862, Abcam, Cambridge, UK), anti-PPARγ (1:1000, ab209350, Abcam, Cambridge, UK), anti-USF1 (1:1000, #ab180717, Abcam, Cambridge, UK), anti-ATGL (1:1000, #ab109251, Abcam, Cambridge, UK), anti-FSP27 (1:1000, #ab213693, Abcam, Cambridge, UK), anti-PGC1α (1:1000, #ab191838, Abcam, Cambridge, UK), anti-LXRα(1:1000, #ab106464, Abcam, Cambridge, UK), CAV-1(1:1000, #ab2910, Abcam, Cambridge, UK), HSL(1:1000, #ab45422, Abcam, Cambridge, UK), FABP1 (1:1000, #ab222517, Abcam, Cambridge, UK), anti-FAS (1:1000, #3180S, Cell Signaling, Danvers, MA, USA), anti-CD36 (1:1000, #74002, Cell Signaling, Danvers, MA, USA), anti-SCAP (1:1000, #13102S, Cell Signaling, Danvers, MA, USA), anti-pAMPKα (1:2000, #2535S, Cell Signaling, Danvers, MA, USA), anti-AMPKα(1:1000, #2532, Cell Signaling, Danvers, MA, USA), anti-ACC (1:500, #3662S, Cell Signaling, Danvers, MA, USA), anti-

INSIG2 (1:1000, #PA5109863, Invitrogen, Camarillo, USA), anti-FATP2 (1:1000, #MA5-50447, Invitrogen, Camarillo, USA), anti-GAPDH (1:5000, #5174, Cell Signaling, Danvers, MA, USA) and anti-Actin (1:8000, #mab1501, Sigma-Aldrich, St. Louis, USA). The membrane was subsequently incubated with horseradish peroxidase-conjugated secondary antibodies, specifically goat anti-rabbit IgG (1:5000, Millipore, Billerica, USA) or goat anti-mouse IgG (1:5000, Millipore, Billerica, USA). An Amersham Gel Imager (GE Healthcare, Chicago, Il, USA) and Quantity One software (Bio-Rad, Gladesville, NSW, Australia) were used for visualization and quantification of Western blot images. The quantitative results were normalized according to the corresponding GAPDH or ACTIN levels (as an internal control). Western blot analyses were performed on six randomly selected samples from each group, with each sample assayed in duplicate.

2.4 Statistics

Statistical analysis was conducted using SPSS software (V25.0, IBM, Armonk, NY, USA), while outliers were indentified and excluded using a Boxplot. The Kolmogorov-Smirnov test was used to assess data distribution. For normally distributed data, a two-way ANOVA (Exercise × Risperidone) was performed, followed by post-hoc least significant difference tests. For non-normally distributed data, a nonparametric Kruskal-Wallis H-test was used, followed by a post-hoc Mann-Whitney U-test with Bonferroni correction [36, 37]. Results are presented as the mean ± SEM, with $p < 0.05$ considered statistically significant.

3. Results

3.1 Hepatic Lipid Synthesis

The risperidone-treated sedentary group showed increased protein expression of INSIG2, FAS and USF1, which was reduced by exercise intervention ($p < 0.05$; Figures 1A, 1B, 1C). SCAP protein levels were increased in risperidone-treated groups ($p < 0.05$; Figure 1D). LXRα levels was decreased by risperidone treatment in the sedentary groups ($p < 0.05$; Figure 1E). Voluntary exercise tended to increase the ratio of pAMPK/AMPK, while the co-treatment of risperidone and exercise further upregulated the ratio of pAMPK/AMPK ($p < 0.05$; Figure 1F) significantly. There were no differences in precursor SREBP1c, mature SREBP1c, and its downstream target SCD1 and ACC1 (Figures 1G, 1H, 1I, 1J).

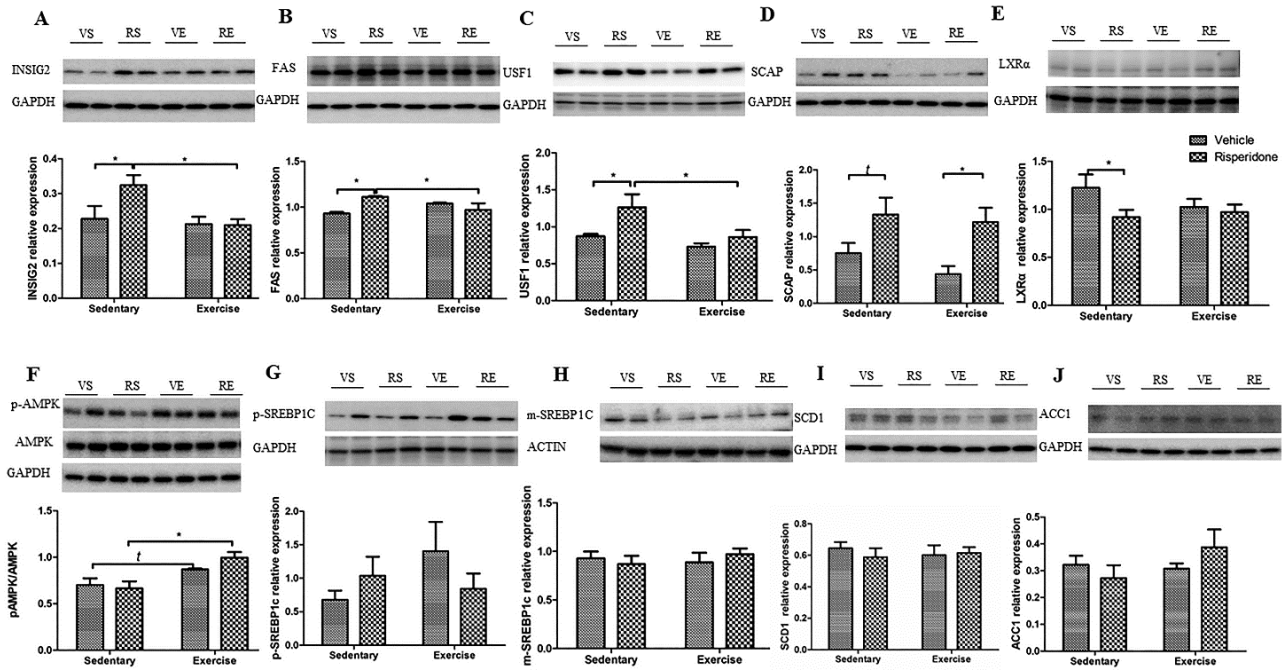

Figure 1 The effects of risperidone and exercise intervention on the protein expression associated with hepatic lipogenesis. Western blot images and relative expression of (A) INSIG2, (B) FAS, (C) USF1, (D) SCAP, (E) LXRα, (F) pAMPk/AMPK, (G) p-SREBP1C, (H) m-SREBP1C, (I) SCD1, and (J) ACC1. Data represent Mean ± SEM (n = 6/group). Abbreviations: VS, Vehicle + Sedentary group; RS, Risperidone + Sedentary group; VE, Vehicle + Exercise group; RE, Risperidone + Exercise group. *, $p < 0.05$; t, $0.05 < p < 0.1$ *vs* VS.

3.2 Hepatic Lipid Uptake and Storage

Hepatic levels of PPARγ and CD36 were increased by risperidone treatment and subsequently reversed by exercise intervention ($p < 0.05$; Figures 2A, 2B). FATP2 expression was reduced by exercise intervention in all groups treated with either vehicle or risperidone ($p < 0.05$; Figure 2C). FSP27 expression was decreased by exercise intervention ($p < 0.05$; Figure 2E). No significant differences were observed in CAV-1 (Figure 2D) and FABP1 levels (Figure 2F).

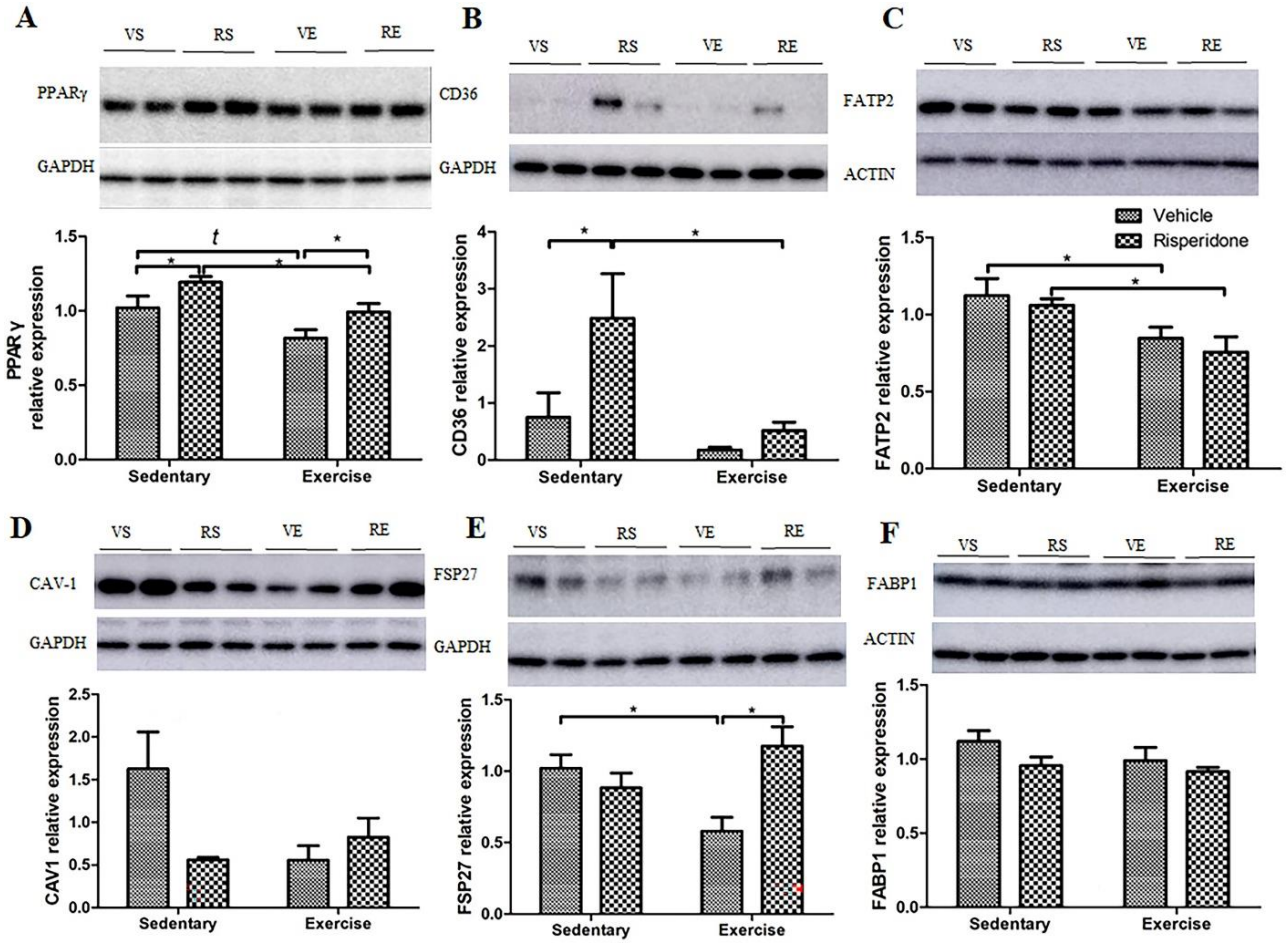

Figure 2 The effects of risperidone and exercise intervention on the protein expression associated with fatty acid uptake. Western blot images and relative expression of (A) PPARγ, (B) CD36, (C) FATP2, (D) CAV-1, (E) FABP1, and (F) FSP27. Data represent Mean ± SEM (n = 6/group). Abbreviations: VS, Vehicle + Sedentary group; RS, Risperidone + Sedentary group; VE, Vehicle + Exercise group; RE, Risperidone + Exercise group. *, $p < 0.05$; t, $0.05 < p < 0.1$ *vs* VS.

3.3 Hepatic Lipolysis

Although no significant difference was detected between the Risperidone + Sedentary and Vehicle + Sedentary groups, hepatic ATGL and HSL protein levels were higher in the Risperidone + Exercise than Risperidone + Sedentary groups ($p < 0.05$; Figures 3A, 3B).

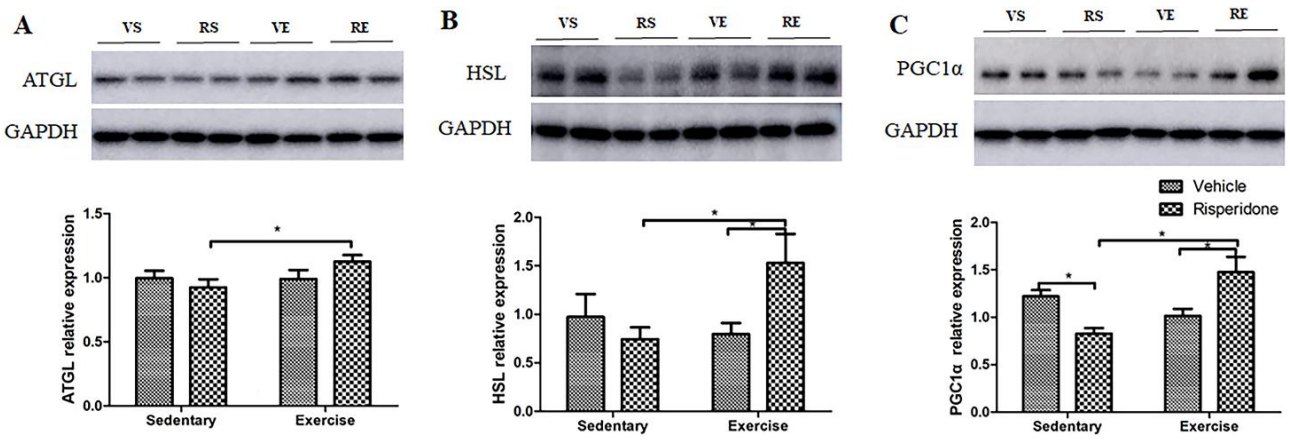

Figure 3 The effect of risperidone and exercise intervention on the protein expression related to β-oxidation and lipolysis. Western blot images and the relative expression of (A) ATGL, (B) HSL, and (C) PGC1α. Data represent Mean ± SEM (n = 6/group). Abbreviations: VS, Vehicle + Sedentary group; RS, Risperidone + Sedentary group; VE, Vehicle + Exercise group; RE, Risperidone + Exercise group. *, $p < 0.05$.

3.4 Hepatic Fatty Acid Oxidation

Reduced PGC1α expression was noted in the risperidone-only treatment group ($p < 0.05$) that was reversed *via* exercise intervention ($p < 0.05$; Figure 3C).

4. Discussion

Our previous study found that exercise intervention reduces risperidone-induced elevations in plasma triglyceride levels, white adipose tissue weight, and insulin levels, suggesting altered lipid metabolism [10]. The current study provides evidence that 4 weeks of voluntary exercise ameliorated risperidone-induced hepatic lipid metabolic disturbances in female juvenile rats. This was achieved by downregulating signalling pathways involved in fatty acid synthesis (*via* USF1/FAS signalling) and uptake (*via* PPARγ/CD36 signalling), while upregulating pathways associated with lipid breakdown (*via* ATGL/HSL signalling) and enhancing the expression of key regulators of fatty acid oxidation (particularly PGC1α signalling).

AMPK regulates lipid metabolism by activating hepatic AMPK signaling, which inhibits the expression and activity of lipogenic regulators such as SREBP1—a critical transcription factor for *de novo* lipogenesis. Impairment of this regulatory axis contributes to lipid metabolism disorders [38]. It is agreed with the reports that 4 weeks of risperidone treatment in this study did not change hepatic SREBP1c expression and activation of AMPK [39, 40]. It is noteworthy that the four-week exercise intervention increased the pAMPK/AMPK ratio in the risperidone treatment group. Exercise training is able to reduce triglyceride synthesis in muscle, white adipose tissue, and liver *via* the p-AMPK pathway [41, 42]. In this context, exercise intervention may confer benefits in decreasing triglyceride synthesis *via* the activation of the pAMPK pathway, although risperidone-enhanced lipid synthesis does not occur through this pathway.

It has been reported that risperidone resulted in the overexpression of SREBP1c, SCAP, and its downstream lipogenic targets (SCD1, ACC1, and FAS), while downregulating INSIG2 [43, 44]. Only FAS expression was significantly upregulated by risperidone treatment in this study. It has been

reported that risperidone could induce FAS without necessarily activating SREBP1c [39], while other transcription factors (e.g., LXR and USF1) may regulate FAS expression through both SREBP1-dependent and independent pathways [45-47]. In fact, USF1 has been reported to mediate insulin-induced FAS expression [45]. USF1 and FAS expression levels were upregulated by risperidone treatment in this project, while this increase was reversed by exercise intervention, similar to the changes observed in plasma insulin levels [32]. It suggests that exercise ameliorates risperidone-induced disturbances in lipogenesis through insulin/USF1/FAS signalling. Additionally, the risperidone-only treatment group exhibited increased INSIG2 expression and reduced LXRα expression, which does not match with previous findings [43, 44]. The discrepancy may be attributed to differences in animal gender, age, and treatment duration.

Free fatty acids from blood are one of the primary sources of liver-derived fatty acids [48, 49]. Several proteins facilitate the influx of long-chain fatty acids into the liver, including scavenger receptor CD36, FATP2, and FABP1 [15]. In addition, FSP27 enhances triglyceride accumulation [50]. CD36 was found to be increased in animal models with hepatic steatosis, as well as patients with nonalcoholic fatty liver disease [51, 52]. It remains unclear whether risperidone affects hepatic CD36 expression, while exercise intervention has been shown to suppress hepatic CD36 expression in mice with non-alcoholic steatohepatitis [53]. In addition, CD36 is a transcriptional target of PPARγ [15, 54], which regulates liver triglyceride homeostasis [55]. We showed that risperidone increased levels of hepatic CD36 and PPARγ proteins, while exercise intervention decreased their levels. These results suggested that exercise could alleviate risperidone-induced hepatic lipometabolic disturbances through the PPARγ/CD36 pathway. Our study also observed that hepatic levels of PPARγ, CD36, and FAS proteins increased at 4 weeks, which aligns with findings from previous reports [56, 57].

FATP2 is highly expressed in the liver, contributing to 40% of long-chain fatty acid uptake [58]. FABP1 facilitates the uptake, transport, and metabolism of fatty acids [59]. 12-week treatment of olanzapine has been reported to upregulate hepatic FATP2 and FABP1 expression [60], whereas no difference was detected in the risperidone-treated groups in this study. Interestingly, exercise intervention reduced FATP2 and FSP27 levels. These results suggested that 4-weeks of voluntary exercise may reduce hepatic fatty acid uptake and lipid storage in juvenile rats.

In addition to synthesis and uptake, fatty acids can be released from the hydrolysis of TGs, which is initiated by ATGL. ATGL and HSL are key enzymes in triacylglycerol catabolism, providing fatty acids [61] and promoting oxidation [62]. It is agreed with our results that 8-week aerobic training has been reported to improve hepatic steatosis by promoting ATGL expression [63]. In our study, 4 weeks of voluntary exercise increased hepatic ATGL and HSL protein expression in rats treated with risperidone, suggesting that ATGL and HSL may contribute to improved hepatic lipid metabolism through exercise. It is worth noting, however, that phosphorylated HSL (pHSL) and the pHSL/HSL ratio also play essential roles in lipolysis; future studies may benefit from evaluating these parameters. Most fatty acids from various sources will undergo mitochondrial β-oxidation to produce CO_2 and ketone bodies (a main end product of hepatic FA catabolism) [64]. PGC-1α enhances FA oxidation and reduces triacylglycerol storage and secretion in the liver [65]. It has been documented that PGC-1α expression was downregulated by was decreased olanzapine in brown adipose tissue [66], while PGC-1α expression is increased by voluntary exercise in the liver [67]. Our findings demonstrated that voluntary exercise reversed risperidone-induced downregulation of hepatic PGC-1α expression. Given the established role of PGC-1α in metabolic regulation, this

alteration suggests a potential mechanism by which voluntary exercise attenuates risperidone-induced lipid accumulation; however, direct measurements of fatty acid oxidation rates are still needed and should be addressed in future studies.

PPARα, CPT1A and HMGCS2 play critical roles in hepatic fatty acid β-oxidation and ketogenesis [13, 16, 68]. Previous studies have indicated that both exercise and second-generation antipsychotics can affect their expression levels [69, 70]. However, our previous study found that only PPARα expression was lower in the risperidone-only group [10]. It is possible that four weeks of exercise intervention is insufficient to alter their expression levels.

5. Conclusions

Our previous study demonstrated that chronic risperidone treatment in juvenile rats enhanced white adipose tissue accumulation, and upregulated fasting levels of triglyceride and insulin, leading to disturbances in lipid metabolism, while a 4-week voluntary exercise intervention ameliorated these effects [10]. This study reveals that voluntary exercise may mitigate risperidone-induced lipid disturbances through multiple mechanisms, including suppression of fatty acid synthesis *via* the insulin/USF1/FAS pathway, reduction of hepatic fatty acid uptake through the PPARγ/CD36 pathway, and up-regulation of PGC1α expression, which is closely associated with β-oxidation potential. However, several limitations should be considered. Firstly, the lipid metabolism in drug-naive patients with mental disorders is different from that in the healthy population [71, 72]. Therefore, an animal model for psychotic disorders will be valuable in future studies to investigate the mechanisms for risperidone and exercise interventions on lipid metabolism in patients with mental disorders. Secondly, the effects of voluntary exercise would be more pronounced if the running wheel were installed in their home cage, allowing the rats to access it at any time rather than just for 3 hours per day, as in this study. Thirdly, the present study does not include histological evaluation of hepatic lipid deposition (e.g., Oil Red O staining) or assessments of liver function enzymes (such as serum ALT and AST), which should be addressed in future investigations. Additionally, it is worth noting that direct functional evidence of fatty acid oxidation, such as measurement of mitochondrial oxygen consumption or β-oxidation enzyme activity, was also not assessed in this study. Our conclusions regarding lipid catabolism are therefore primarily based on the expression levels of PGC-1α and relevant signalling proteins. Future studies incorporating comprehensive liver function assessments will be valuable to determine whether these molecular changes translate into corresponding alterations in hepatic functions. Overall, this project underscores the prospects of clinical exercise interventions in mitigating metabolic abnormalities in children/adolescents undergoing risperidone treatment. In addition to hepatic lipid regulation, white adipose tissue also plays a crucial role in lipid metabolism. Future studies will aim to investigate how risperidone and voluntary exercise modulate lipid metabolic pathways in adipose tissue. Furthermore, future research should explore the long-term benefits of lifelong exercise and its potential impacts during adolescence on adult health, particularly in juveniles with mental disorders.

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Author Contributions

WY and CD designed the experiments. WY, and JL performed the experiments. WY and CD analyzed the data. WY prepared the initial draft of the manuscript. CD, WY, and JL revised the manuscript. All authors commented on and approved the final draft.

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Competing Interests

The authors have declared that no competing interests exist.

AI-Assisted Technologies Statement

During the preparation of this work, the authors used Microsoft Copilot for grammar checks to improve the readability and language of the work. The authors are fully responsible for the content of the published article.

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