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Original Research

Effects of Early Risperidone Treatment on Metabolic Parameters in Socially Isolated Rats—Implication of Antipsychotic Intervention across Developmental Stages of Schizophrenia

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Abstract

Background: Second-generation antipsychotics (SGAs) is thought responsible for the metabolic abnormalities of schizophrenic patients, however, some untreated schizophrenic patients had already developed problems with glucose metabolism. The present study examined the hypothesis that schizophrenia itself but not risperidone, an extensively employed SGA, is accountable for metabolic abnormalities. **Methods**: A 56-day risperidone regimen (1 mg/kg/day) was employed for rats of social isolation rearing (SIR) beginning at different developmental stage (28 or 56 days after weaning, i.e., adolescent and young adulthood, respectively). Metabolic parameters including body weight, systolic blood pressure (SBP), triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, and plasma glucose were measured at baseline, 28, and 56 days of the regimen. Oral glucose tolerance test (OGTT) was performed at the end of the regimen. Insulin function was evaluated by area under the curve (AUC) of OGTT, homeostasis model assessment-insulin resistance (HOMA-ir), and Matsuda index. **Results**: Our results demonstrated that: (i) SIR rats presented higher body weight, plasma triglyceride, and HOMA-ir than social controls. (ii) Higher insulin resistance was specifically presented in young adult rather than adolescent SIR rats. (iii) Adolescent drugged rats showed a lower level of LDL in day 28 of the regimen than young adult. Risperidone led to a lower LDL level in only young adult IR rats in day 56 than undrugged rats. (iv) SIR-induced dysregulation of insulin can be reversed by chronic risperidone treatment beginning at adolescence but not young adulthood. **Conclusions**: Our findings support the primary role of schizophrenia in metabolic abnormalities and risperidone appear beneficial when administered earlier.

Keywords: developmental hypothesis; early antipsychotic intervention; metabolic abnormalities; schizophrenia; social isolation

1. Introduction

Patients of schizophrenia experience a long-term suffering of multidimensional malfunctions, mostly including distortions of thought and perception (positive symptoms), lack of motivation and agility (negative symptoms), and cognitive deterioration as time lapses [1]. Treatment of schizophrenia obtains a great achievement after the emergence of antipsychotics in the last century. In particular, the extensive use of SGAs proves helpful in treating schizophrenia by relieving both the positive and negative symptoms of patients and with a lower risk of extrapyramidal side effects (EPS) [2]. However, high risk of metabolic abnormalities and its associated adverse cardiovascular effects leads to poor drug compliance and increased mortality rate [3,4]. It raises the concerns about the pros and cons of SGAs [5].

While SGA-induced metabolic abnormalities are considered among of the most serious long-term side effects in treating schizophrenia, studies also revealed that unhealthy lifestyle and diet habit of schizophrenic patients contribute to the metabolic abnormalities too [6,7]. The patients are used to having unhealthy diet, rich in saturated fats and poor in fiber and fruit, which in turn promotes development or worsens the metabolic abnormalities in predisposed individuals [8]. In other words, it is possible that the treatment of SGAs is not the primary reason of metabolic abnormalities; the causative relationships between the progress of schizophrenia and the antipsychotic intervention are worth to clarify.

Increasing evidence obtained from human studies with small sample sizes demonstrated that untreated schizophrenic patients in their first episode may have problems with glucose metabolism already [9–12], raising the possibility that the metabolic problem is among the initial symptoms of schizophrenia. To elaborate the assumption, neurodevelopmental model of pathoetiology of schizophrenia is worth investigating, as it stresses the primary impact of the disorder can be traced back to patients' juvenile and adolescent stages [13]. It is interesting to know whether

the metabolic dysfunctions occur during the development of schizophrenia and if they can be corrected by early antipsychotic intervention.

The aim of the present study is twofold. First, we examined the link between schizophrenia and metabolic abnormalities in drug-naïve, social isolation rearing (SIR) rats. Second, we determined whether the metabolic changes, if any, are relevant to the developmental stage of schizophrenia with or without the intervention of risperidone, a broadly employed SGA. SIR rats have profound psychological, behavioral and neurochemical abnormalities in their adulthood and are commonly used to model schizophrenia in the context of the developmental hypothesis [14,15]. The rats are raised socially isolated since their weanling, they are allowed to see, smell and hear other rats but not to have physical contact with them. The hallmark feature of SIR rats in modelling schizophrenia is that their impaired acoustic sensorimotor gating deficit of prepulse inhibition (PPI), one of the characteristics of schizophrenia and which can be corrected by antipsychotics [16].

Previously we demonstrated that risperidone was more beneficial when administering earlier (i.e., adolescence) than later (i.e., young adulthood) in correcting the impairment of PPI in SIR rats [5]. In the present study, SIR rats that received risperidone intervention at different age would be measured for their metabolic parameters [blood pressure, body weight, plasma levels of triglyceride, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and glucose]. Insulin function was evaluated after oral glucose tolerance test (OGTT), by calculating homeostasis model assessment-insulin resistance (HOMA-ir), Matsuda index, and area under the curve (AUC) of glucose [17]. The present study delineates the causal relationships among metabolic abnormalities, the intervention of antipsychotics, and the age of schizophrenic patients to receive medication, thus highlighting the importance of intervention timing during the developmental of schizophrenia.

2. Methods

2.1 Subjects

Male Sprague-Dawley rats (BioLASCO, Taiwan) of the same batch were used in all experiments. The rats were 21–23 days old and had been weaned upon arrival at the animal center of the National Defense Medical Center (NDMC, Taipei, Taiwan). Rats in the SIR group were housed singly (cage size: 43 × 22 × 21 cm^3). They could see, hear, and smell others but were kept separate and denied physical contact. The control group for SIR was a social rearing (SOC) group. These rats were from the same batch as the SIR rats but were reared socially (n = 2 for each cage) in the same sized cage as the SIR rats. All rats were housed in a temperature (21–25 °C)- and humidity (40–60%)-controlled holding facility with 12 hour light/dark cycles (light on from 0700 to 1900) and received food and water *ad libitum*. All experimental procedures were made to minimize animal suffering and reduce the number of animals used and were approved by the Laboratory Animal Center from the National Defense Medical Center (IACUC-11-237).

2.2 Experimental Design

(1) After weaning (3 weeks postnatal age), 64 rats were randomly and equally assigned to the IR or SOC group. Pharmacological manipulation (risperidone, 1 mg/kg/day or saline vehicle) was introduced when rats were in their adolescence (7 weeks old, W7) or young adulthood (11 weeks old, W11). The administration regimen was continued for 8 weeks.

(2) Body weight, systolic blood pressure and metabolic measures, including blood levels of TC, LDL, HDL, glucose and insulin, were taken in the same rats at the midpoint and at the end of the study (i.e., 4 and 8 weeks after beginning treatment). An OGTT was performed on each rat at the end of the treatment regimen. All the analyses of all animals were conducted at the same time of the day (within one-hour range) to minimize the confounding effects of circadian oscillations.

2.3 Blood Pressure Measurement

The systolic blood pressure (SBP) of the rats was measured with the tail-cuff method using an automatic monitoring system (UR-5000; UEDA, Tokyo, Japan).

2.4 OGTT and Insulin Resistance and Sensitivity

The OGTT was performed 2 days after the last risperidone injection. Rats were orally administered a 20% glucose solution (2 g/kg), and the blood samples were collected from the tail vein, in which the rats were anesthetized under 5% isoflurane during the procedure, at 0 (before the glucose solution administered), 30, 60, 90, 120, and 150 min after a 12-hour fast to measure plasma glucose and insulin. Insulin resistance was indexed by the AUC of glucose under OGTT for 150 min and HOMA-ir of fasting glucose and insulin. Insulin sensitivity was indexed with the Matsuda method (1999) [17]. The Matsuda method was first advocated by Dr. Matsuda and Prof. DeFronzo [17] to provide a good index to evaluate whole body physiological insulin sensitivity from the data obtained by oral glucose tolerance test. The Matsuda index can be obtained from a WEB calculator in EXCEL linked by *https://view.officeapps.live.com/op/view.aspx?src=http%3A%2F%2Fmmatsuda.diabetes-smc.jp%2FMatsudaIndex.xls&wdOrigin=BROWSELINK, or for detail explanation, see http://mmatsuda.diabetes-smc.jp/english.html*

2.5 Biochemical Analysis

Plasma glucose levels were measured with a blood sugar analyzer (YSL, Model 2300 plus, Yellow Springs, OH, USA) using the glucose oxidative method. Plasma lev-

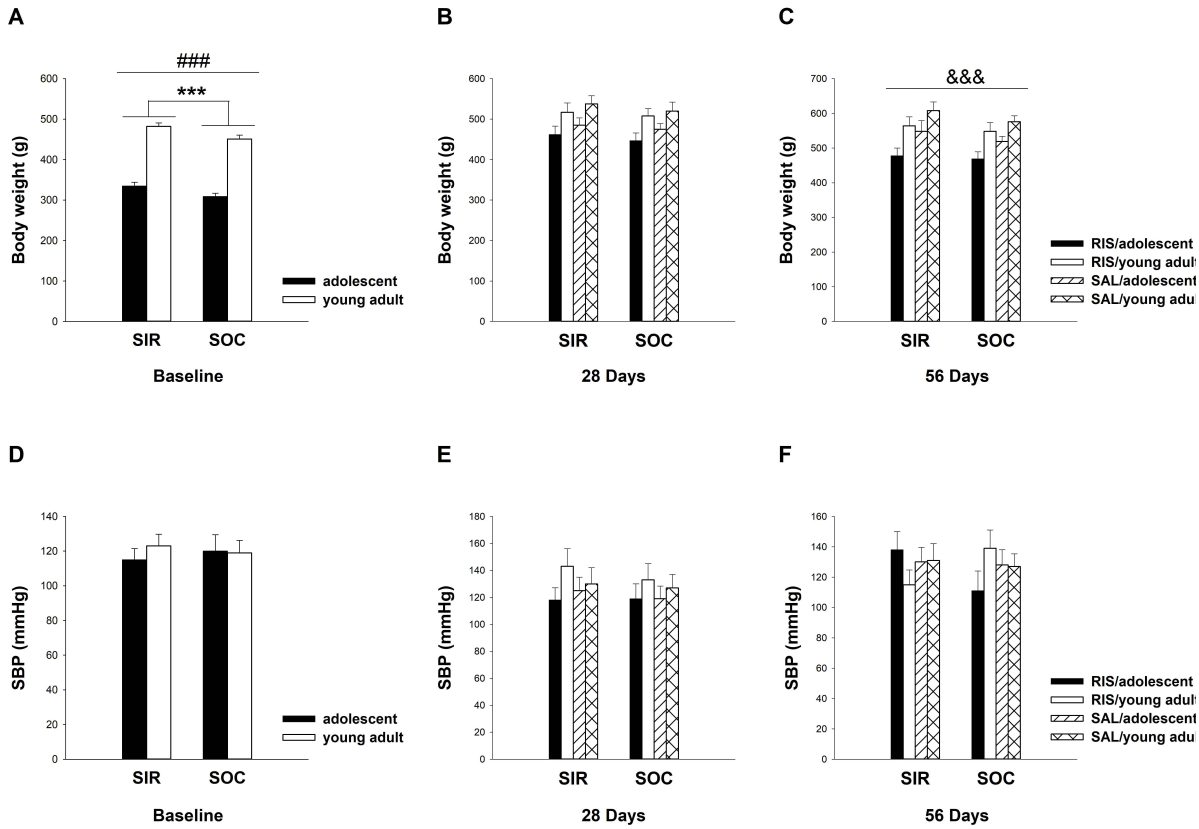

Fig. 1. Effects of treatment, timing, and rearing condition on body weight and SBP. SIR rats are significantly heavier than social controls (A) (N = 12 in each of the following conditions: IR/adolescent, IR/young adult, SOC/adolescent, SOC/young adult). Rats receiving saline vehicle were heavier than those receiving risperidone for 56 but not 28 days (B,C) (N = 6 for each subgroup). No significant change in systolic blood pressure (SBP) in baseline (D) (N = 12), 28 days, and 56 days (E,F) (N = 6 for each subgroup). Data are represented as group averages + SEM. *** $p < 0.001$, main effect of rearing; ### $p < 0.001$, main effect of timing; &&& $p < 0.001$, main effect of treatment.

els of triglyceride, total cholesterol (TC), and HDL were assayed with an automatic biochemical analyzer (Cobas Mira, Washington, USA) using the enzymatic colorimetric method. LDL was calculated according to the formula [LDL = TC – HDL – (triglyceride/5)]. Plasma insulin levels were analyzed with a commercial rat ELISA kit (Mercodia AB, Uppsala, Sweden) and measured by Biotek Synergy HT Microplate Reader (Biotek Instruments Inc., Winooski, VT, USA) at 450 nm.

2.6 Drug

Risperidone (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in saline vehicle. The drug was prepared to produce a total injection volume of 1.0 mL/kg and was injected subcutaneously (sc) at 10:00–11:00 AM. Dose of risperidone used in this study has previously been shown to recover PPI in rats [18]. Also, the conversion factor based on the 'animal to human equivalent dose' is about 6.17 for rats [19], thus the equivalent dose for human is about 0.16 mg/kg. It goes to 4 mg/day in a 25-kg child, within the dose of risperidone for adolescent schizophrenia (range from 1 to 4.5 mg/day) [20].

2.7 Statistical Analyses

Statistical analyses were performed across the groups by analysis of variance (ANOVA) using REARING, TREATMENT and TIMING as between-subject factors. For further analyses, a *post-hoc* multiple comparison of Tukey method was employed. Where appropriate, a *priori* comparison was conducted with a Student-*t* test. For brevity, *F*-values are only provided for significant effects. A *p* value of <0.05 was considered statistically significant.

3. Results

3.1 Body Weight and Blood Pressure

For body weight, young adult rats (i.e., 8 weeks after the isolation procedure) were heavier than adolescent rats (i.e., 4 weeks after the isolation procedure) at baseline [TIMING, $F(1,44) = 378.13$, $p < 0.001$], and the IR rats were significantly heavier than social controls (330 g versus 300 g, respectively). [R0EARING, $F(1,44) = 14.3$, $p < 0.001$]. After RIS regimen for 56 days, rats receiving saline vehicle were heavier than those receiving risperidone [TREATMENT, $F(1,40) = 14.4$, $p < 0.001$]. For SBP, there

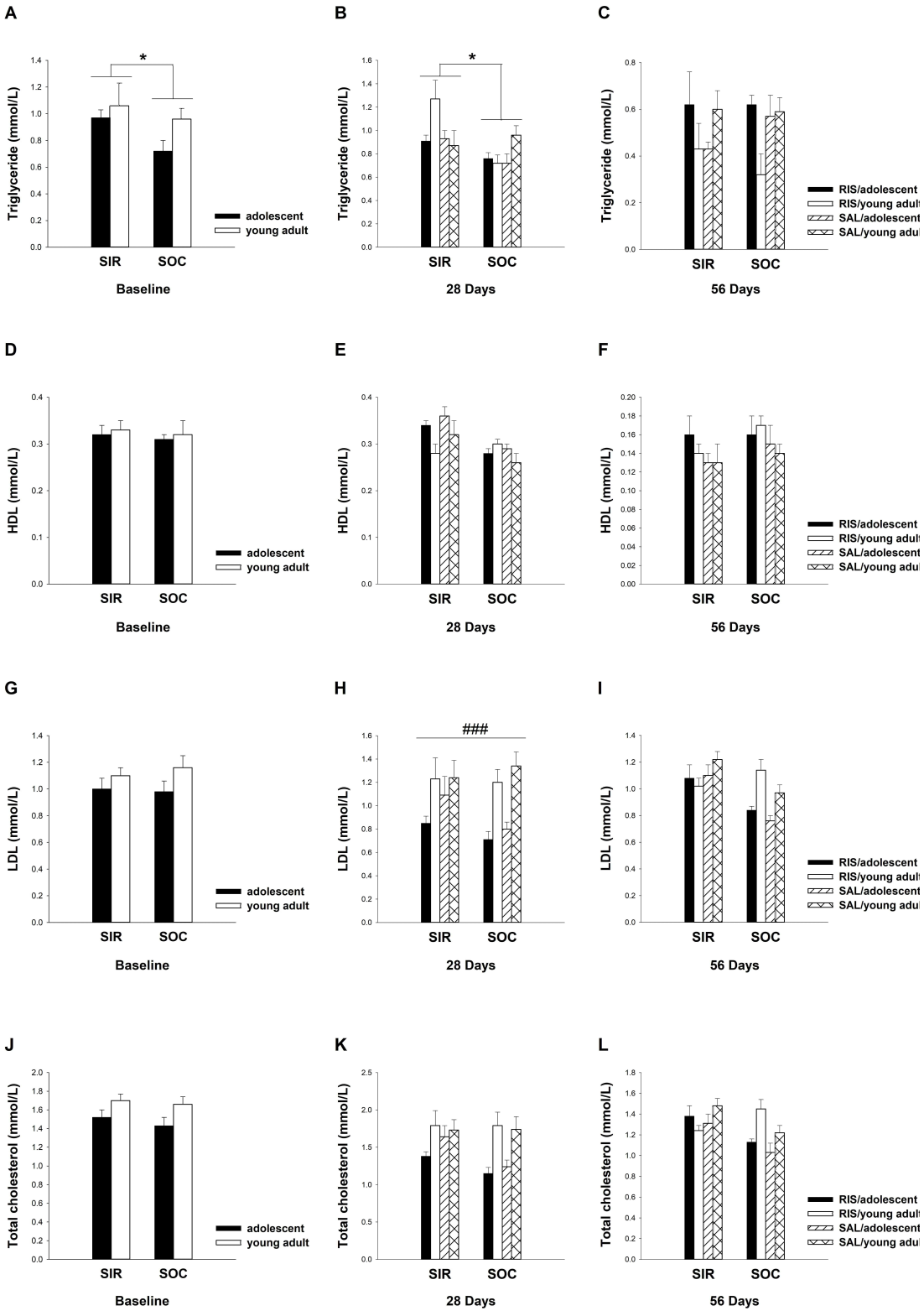

Fig. 2. Effects of treatment, timing, and rearing condition on triglyceride, HDL, LDL, and total cholesterol. SIR rats have higher triglyceride level than SOC rats (A) (N = 12 in each of the following conditions: IR/adolescent, IR/young adult, SOC/adolescent, SOC/young adult, each condition separates to two subgroups, RIS and SAL, see B and C). No significant change in triglyceride 56 day, HDL baseline, 28 and 56 days (D–F), LDL baseline and 56 days (G,I), and total cholesterol (J–L). For A, D, G, J, N = 12 for each subgroup. For others, N = 6 for each subgroup. Adolescent rats in both rearing conditions showed a lower level of LDL in day 28 (H) (N = 6 for each subgroup). Data are represented as group averages + SEM. * $p < 0.05$, main effect of rearing; ### $p < 0.001$, main effect of timing.

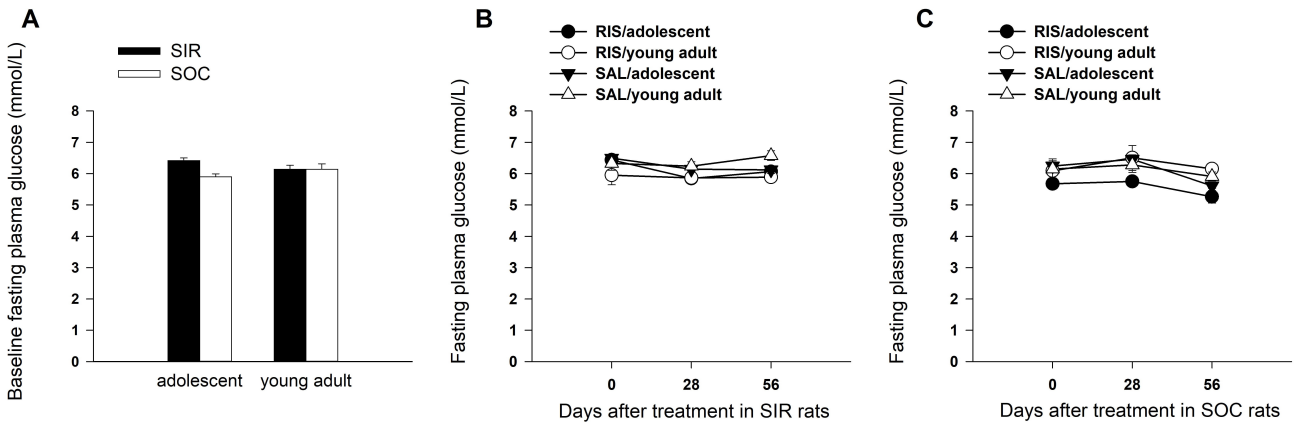

Fig. 3. Effects of treatment, timing, and rearing condition on baseline fasting plasma glucose. SIR rats have a higher level of fasting plasma glucose than social controls at baseline (N = 12 in each of the following conditions: IR/adolescent, IR/young adult, SOC/adolescent, SOC/young adult) at their adolescence but not young adulthood (A). Fasting plasma glucose is unaffected by early intervention of risperidone treatment at Days 28 and 56 (B,C) (N = 6 for each subgroup). Data are represented as group averages + SEM.

were no effects of REARING, TIMING, or TREATMENT at baseline or after the drug regimen. Interactions of REARING × TIMING were found at 28 days [$F(1,40) = 6.04$, $p = 0.020$] and 56 days [$F(1,40) = 14.1$, $p = 0.001$] in the RIS group (Fig. 1).

3.2 Triglyceride, HDL, TC, and LDL

Regarding triglyceride, there was a main effect of REARING at baseline [$F(1,44) = 4.23$, $p = 0.045$] and after 28 days of treatment [$F(1,40) = 7.12$, $p = 0.011$]. HDL was not affected by any of the factors. For LDL, adolescent rats in both rearing conditions showed a lower level of LDL in day 28 of the regimen [for TIMING, $F(1,40) = 18.3$, $p < 0.001$]. After 56 days of treatment, compared to saline vehicle, RIS led to a lower LDL level in young adult IR rats [$F(1,40) = 7.66$, $p = 0.009$ and $F(1,40) = 8.88$, $p = 0.005$, for REARING × TIMING in RIS group and REARING × TREATMENT in young adult group, respectively]. For TC, adolescent SOC rats had a lower level of TC on treatment day 28 [REARING × TIMING in RIS group, $F(1.40) = 16.9$, $p < 0.001$], and this phenomenon persisted across the experiment [for day 56: $F(1,40) = 5.94$, $p = 0.019$, for REARING × TIMING in RIS group] (Fig. 2).

3.3 Glucose and Insulin

For glucose, fasting plasma glucose levels were higher in SIR rats than in social controls at adolescence [REARING × TIMING: $F(1, 44) = 4.272$, $p = 0.045$], but not at young adulthood at baseline (Fig. 3).

Regarding insulin resistance, the AUC of glucose under OGTT was unaffected by REARING, TIMING, TREATMENT and their interactions. In contrast, a higher HOMA-ir was found in IR young than SOC rats [REARING, $F(1,40) = 4.80$, $p = 0.034$]. After risperidone treatment, adolescent IR rats had a lower HOMA-ir than their young adult controls [$t(10) = 2.03$, $p = 0.031$, *a priori* comparison]. Further analysis also showed that adolescent IR rats that had been treated with risperidone also had a lower HOMA-ir than their vehicle controls [$t(10) = 2.38$, $p = 0.019$, *a priori* comparison]. These data indicated that the reduction of HOMA-ir only occurred in IR rats received the drug treatment at their adolescent. Finally, regarding insulin sensitivity, there were no effects of REARING or TREATMENT. However, adolescent rats had a higher Matsuda index than young adult rats [TIMING, $F(1,40) = 7.10$, $p = 0.010$] (Fig. 4).

4. Discussion

Although in their first episode, schizophrenic patients may appear metabolic problems [9,10,21], clinical approach becomes difficult to clarify the longitudinal relationship between schizophrenia and metabolic abnormalities, since patients are generally unable keep drug naïve throughout the full course of the disorder. In the present study, SIR rats presented higher body weight, plasma triglyceride, and HOMA-ir than social controls before the risperidone intervention. Thus the occurrence of metabolic abnormalities cannot be entirely ascribed to the intervention of antipsychotics.

For schizophrenia, a postnatal, development process is required for the full-blown presentation of its symptoms, including metabolic/energy dysregulation [22]. Thus the treatment needs to consider patients' age to receive the treatment. In the present study, we began the risperidone regimen at to two different ages, adolescence (W7) and young adulthood (W11). As the regimen took 8 weeks, thus both groups were in their young adult age when metabolic markers were examined. We found that risperidone early intervention reduced the plasma level of LDL in both SIR rats and social controls in which the LDL of young adult SIR rats were more sensitively to be reduced than their social controls rats following the 56-days risperidone regi-

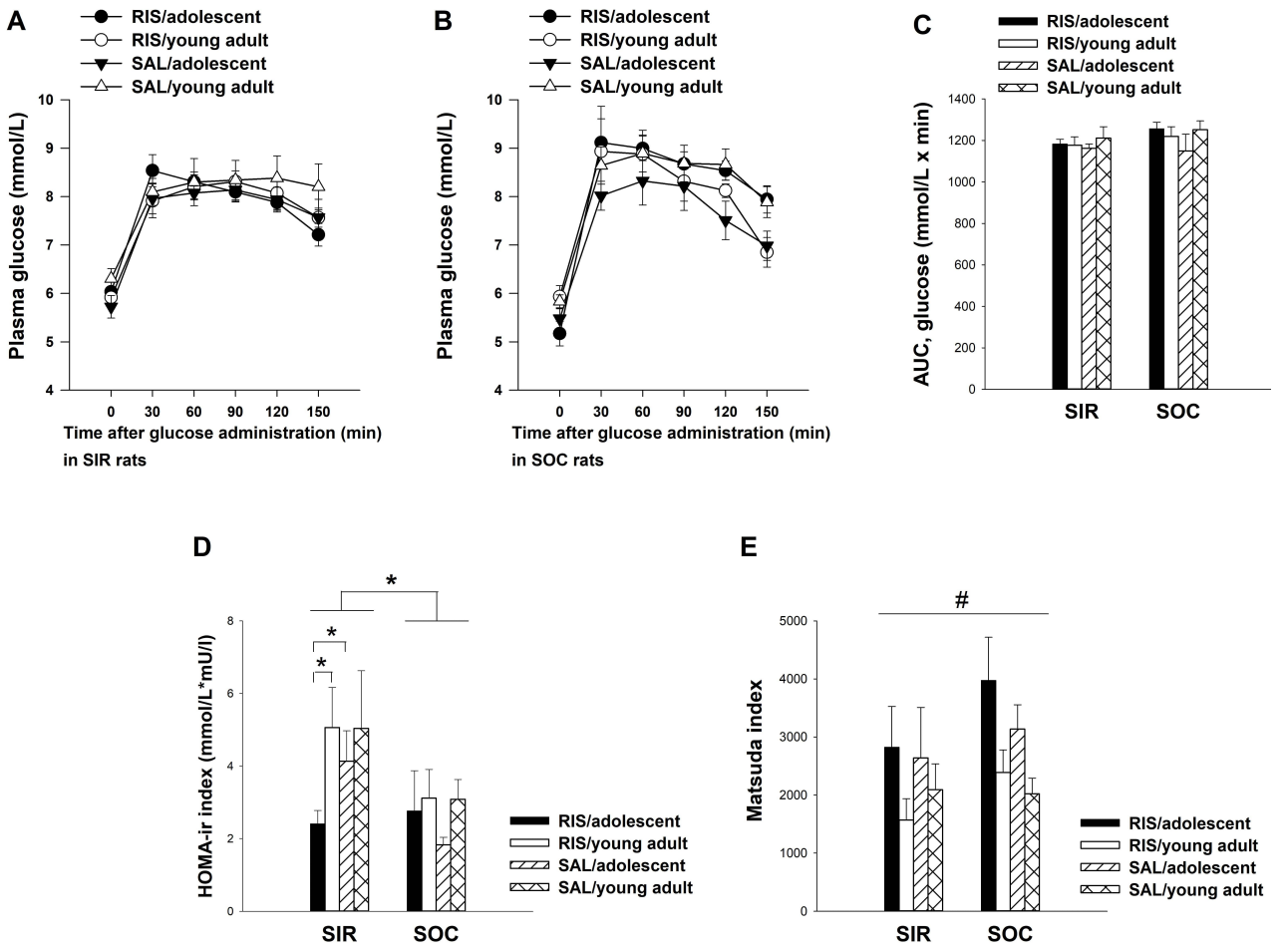

Fig. 4. Effects of treatment, timing, and rearing condition on plasma glucose and HOMA-ir and Matsuda index. SIR plays a primary role in causing glucose metabolic abnormalities at Day 56. In OGTT, TREATMENT and AGE have no effects on plasma glucose in IR (A) or SOC rats (B) or their AUC (C). IR rats have an overall higher HOMA-ir level than social controls (D). Risperidone-treated adolescent IR rats have a lower HOMA-ir level than young adult IR rats. REARING CONDITION and TREATMENT have no effects on insulin sensitivity as measured with the Matsuda index (E), but young rats have an overall higher Matsuda index than older rats (N = 6 for each subgroup). Data are represented as group averages + SEM. * $p < 0.05$; # $p < 0.05$, main effect of timing.

men. It appears that rats in disease model (i.e., SIR) are more beneficial than non-disease model (i.e., social control) following long-term risperidone intervention. This phenomenon is possibly related to the interaction between serotonin function and lipid metabolism during development [23], in which the 5-HT2 antagonism of risperidone was found to reduce LDL level [24], that in turn to increase the brain cell membrane fluidity [25]. As the baseline level of adolescent of LDL is lower than that of young adult rats [23,24,26], the latter is more liable to be reduced. Interestingly, for glucose metabolism, only adolescent SIR rats in our study were benefited. This disparity highlights the interactions between the experience of social isolation and the timing of risperidone intervention in terms of metabolic profile of lipid was different from that of glucose. Note for male rats following post-weanling isolation stress (which is the one employed in the present study), insulin is more sensitive to be affected than LDL [27]. In a clinical study, Karaman and colleagues demonstrated that risperidone increased the serum level of LDL in child and adolescent patients with non-psychotic diagnoses (disruptive behavior disorders, pervasive developmental disorders, and mental retardation) [28]. It appears that the paradoxical effects of risperidone on lipid metabolism might be ascribed to the different origin of pathoetiologies.

Schizophrenic patients have been reported to have insulin malfunction since early 1920s [29], long time ahead the use of antipsychotics. Increasing evidence of the glucose dysfunction in first episode schizophrenic patients exemplifies that glucose metabolism may occur in untreated patients [9,10,21]. The parameters of insulin regulation in our SIR rats revealed a higher HOMA-ir value and unaffected Matsuda index, which is in line with the evidence that first-episode, antipsychotic-naive schizophrenic patients exhibited a greater insulin resistance yet their insulin sensitivity remained unchanged [30].

In addition to that genetic makeup may contribute to the insulin resistance in schizophrenic patients [10,30], we demonstrated that age can be a factor to influence the regulation of insulin performance too, as higher insulin resistance was presented in young adult rather than adolescent IR rats. Further, the reversal of SIR-induced insulin abnormalities by chronic risperidone treatment was also following an age-specific manner; only adolescent SIR rats were beneficial. Previously we demonstrated that age is a crucial factor of antipsychotic effects. Risperidone intervention starting from adolescence was superior to that of adulthood in correcting the SIR-induced PPI deficit of acoustic startle response and apoptotic changes indexed by Bcl-2 and Bax/Bcl-2 ratio [31,32]. At the same dose to correct the SIR-induced PPI deficit [31], risperidone in the present study rectified the SIR-induced insulin abnormalities, strengthening the idea that earlier treatment is expected to achieve greater outcome, and justifying the advantage of SGA in treating abnormalities with a postnatally developmental origin.

Early life stress may induce a series of brain-related, neuronal activities contributing to insulin regulation and energy utilization in adulthood. Hypothalamic neurons are considered the site for antipsychotics to regulate insulin function [33]. The operation of insulin resistance is dependent on (i) the development of paraventricular nucleus (PVN) alpha-melanocyte-stimulating hormone (α-MSH) corticotropin-releasing hormone (CRH) neuron within the hypopthalamic neurocircuit, and (ii) the establishment of a dopamine-related reward evaluation [33,34]. These mechanisms implicate the involvement of dopamine in the SIR-induced abnormalities including insulin dysfunction. Note in the present study effects of risperidone exert largely via the antagonism of 5-HT2 and D2 receptors. Interestingly, evidence reveals that 5-HT2 antagonism significantly decreased insulin response to glucose challenge, whereas D2 antagonism increased the insulin response [35]. The disparity might be relevant to the distinctive occupancy of risperidone on 5-HT2 and D2 receptors. At the dose to exert its antipsychotic effects, risperidone completely occupies 5-HT2 receptors but within a therapeutic range (i.e., 65–80%) of the D2 receptors occupancy [36].

Several concerns/limitations must be mentioned in interpreting our data. First, gender can be a crucial factor to influence metabolic regulations of glucose and lipid [37]. It becomes more complicated according to intervention time of the pharmacological paradigm (i.e., acute versus chronic). For example, Boyda and colleagues revealed a harmful effect of risperidone to increase the insulin resistance in a paradigm of acute administration of the drug in female Sprague-Dawley rats [38]. Only male rats were used in the present study leaves a gap of knowledge of how female rats behave in the same experimental context. Second, the lack of experimental design of multiple doses makes it difficult to ascertain the dose-response risperidone effects. Third, although risperidone has been extensively employed in clinical use, it is unable to represent the whole bunch of SGAs, thus excessive interpretation should be avoided particularly in terms of the early intervention of other SGAs.

5. Conclusions

Schizophrenia is thought as a long-term neurodevelopmental disorder, any possible aberrant brain operations causing developmental impact should be considered [39]. By using a rodent paradigm of social isolation since early life, our findings support the developmental hypothesis and the primary role of schizophrenia in metabolic abnormalities and risperidone appear beneficial when administered earlier. It helps to clarify the relationship between schizophrenia and metabolic abnormalities.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

NST, YPL, YYY and designed the study and wrote the protocol. PSH helped the evaluation of metabolic results. NST and YPL worked for the clinical interpretation. CCL and YPL worked for writing drafts of the manuscript.

Ethics Approval and Consent to Participate

Ethics approval had been granted by the Laboratory Animal Center from the National Defense Medical Center, Taiwan (IACUC-11-237).

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Ved HS, Doshi GM. A Review on Emerging Drug Targets in Treatment of Schizophrenia. Current Drug Targets. 2020; 21: 1593–1605.

[2] Tandon R. Antipsychotics in the treatment of schizophrenia: an overview. The Journal of Clinical Psychiatry. 2011; 72: 4–8.

[3] Newcomer JW. Second-generation (atypical) antipsychotics and

metabolic effects: a comprehensive literature review. CNS Drugs. 2005; 19: 1–93.
[4] Darbà J, Kaskens L, Aranda P, Arango C, Bobes J, Carmena R, *et al*. A simulation model to estimate 10-year risk of coronary heart disease events in patients with schizophrenia spectrum disorders treated with second-generation antipsychotic drugs. Annals of Clinical Psychiatry: Official Journal of the American Academy of Clinical Psychiatrists. 2013; 25: 17–26.
[5] Yang Y, Lu C, Lo S, Peng C, Liu Y. Early antipsychotic intervention and schizophrenia. Medical Hypotheses. 2015; 85: 367–370.
[6] DE Hert M, Schreurs V, Vancampfort D, VAN Winkel R. Metabolic syndrome in people with schizophrenia: a review. World Psychiatry: Official Journal of the World Psychiatric Association (WPA). 2009; 8: 15–22.
[7] Dipasquale S, Pariante CM, Dazzan P, Aguglia E, McGuire P, Mondelli V. The dietary pattern of patients with schizophrenia: a systematic review. Journal of Psychiatric Research. 2013; 47: 197–207.
[8] Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, *et al*. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA. 2004; 292: 1440–1446.
[9] Cohn TA, Remington G, Zipursky RB, Azad A, Connolly P, Wolever TMS. Insulin resistance and adiponectin levels in drug-free patients with schizophrenia: A preliminary report. Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie. 2006; 51: 382–386.
[10] Dasgupta A, Singh OP, Rout JK, Saha T, Mandal S. Insulin resistance and metabolic profile in antipsychotic naïve schizophrenia patients. Progress in Neuro-psychopharmacology & Biological Psychiatry. 2010; 34: 1202–1207.
[11] Saddichha S, Manjunatha N, Ameen S, Akhtar S. Metabolic syndrome in first episode schizophrenia - a randomized double-blind controlled, short-term prospective study. Schizophrenia Research. 2008; 101: 266–272.
[12] Sahpolat M, Ari M. Higher prevalence of metabolic syndrome and related factors in patients with first-episode psychosis and schizophrenia: a cross-sectional study in Turkey. Nordic Journal of Psychiatry. 2021; 75: 73–78.
[13] Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. Lancet (London, England). 2014; 383: 1677–1687.
[14] Fone KCF, Porkess MV. Behavioural and neurochemical effects of post-weaning social isolation in rodents-relevance to developmental neuropsychiatric disorders. Neuroscience and Biobehavioral Reviews. 2008; 32: 1087–1102.
[15] Hall FS. Social deprivation of neonatal, adolescent, and adult rats has distinct neurochemical and behavioral consequences. Critical Reviews in Neurobiology. 1998; 12: 129–162.
[16] Swerdlow NR, Braff DL, Geyer MA. Sensorimotor gating of the startle reflex: what we said 25 years ago, what has happened since then, and what comes next. Journal of Psychopharmacology (Oxford, England). 2016; 30: 1072–1081.
[17] Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care. 1999; 22: 1462–1470.
[18] Zhang M, Ballard ME, Unger LV, Haupt A, Gross G, Decker MW, *et al*. Effects of antipsychotics and selective D3 antagonists on PPI deficits induced by PD 128907 and apomorphine. Behavioural Brain Research. 2007; 182: 1–11.
[19] JW Shin, I-C Seol, CG Son. Interpretation of Animal Dose and Human Equivalent Dose for Drug Development. The Journal of Korean Oriental Medicine. 2010; 31: 1–7.
[20] Bishop JR, Pavuluri MN. Review of risperidone for the treatment of pediatric and adolescent bipolar disorder and schizophrenia. Neuropsychiatric Disease and Treatment. 2008; 4: 55–68.
[21] Kohen D. Diabetes mellitus and schizophrenia: historical perspective. The British Journal of Psychiatry. Supplement. 2004; 47: S64–6.
[22] Agarwal SM, Kowalchuk C, Castellani L, Costa-Dookhan KA, Caravaggio F, Asgariroozbehani R, *et al*. Brain insulin action: Implications for the treatment of schizophrenia. Neuropharmacology. 2020; 168: 107655.
[23] Chattopadhyay A, Paila YD. Lipid-protein interactions, regulation and dysfunction of brain cholesterol. Biochemical and Biophysical Research Communications. 2007; 354: 627–633.
[24] Engelberg H. Low serum cholesterol and suicide. Lancet (London, England). 1992; 339: 727–729.
[25] Diebold K, Michel G, Schweizer J, Diebold-Dörsam M, Fiehn W, Kohl B. Are psychoactive-drug-induced changes in plasma lipid and lipoprotein levels of significance for clinical remission in psychiatric disorders? Pharmacopsychiatry. 1998; 31: 60–67.
[26] Ayesa-Arriola R, Canal Rivero M, Delgado-Alvarado M, Setién-Suero E, González-Gómez J, Labad J, *et al*. Low-density lipoprotein cholesterol and suicidal behaviour in a large sample of first-episode psychosis patients. The World Journal of Biological Psychiatry: the Official Journal of the World Federation of Societies of Biological Psychiatry. 2018; 19: S158–S161.
[27] Krolow R, Noschang C, Arcego DM, Huffell AP, Marcolin ML, Benitz AN, *et al*. Sex-specific effects of isolation stress and consumption of palatable diet during the prepubertal period on metabolic parameters. Metabolism: Clinical and Experimental. 2013; 62: 1268–1278.
[28] Karaman MG, Ozdemir E, Yurteri N, Erdogan A. Risperidone and serum lipid profile changes in child and adolescent patients. Neurology, Psychiatry and Brain Research. 2011; 17: 16–20.
[29] Lorenz WF. Sugar tolerance in dementia praecox and other mental disorders. Archives of Neurology and Psychiatry. 1922; 8: 184–196.
[30] Tomasik J, Lago SG, Vázquez-Bourgon J, Papiol S, Suárez-Pinilla P, Crespo-Facorro B, *et al*. Association of Insulin Resistance With Schizophrenia Polygenic Risk Score and Response to Antipsychotic Treatment. JAMA Psychiatry. 2019; 76: 864–867.
[31] Liu Y, Yang Y, Wan F, Tung C. Importance of intervention timing in the effectiveness of antipsychotics. Progress in Neuro-psychopharmacology & Biological Psychiatry. 2018; 81: 493–500.
[32] Liu Y, Yang S, Yang Y, Wan F, Huang C. Effects of isolation rearing and early antipsychotic intervention on oxidative stress-induced apoptosis and brain-derived neurotrophic factor in hippocampus in a rat model of schizophrenia. Journal of Medical Sciences. 2017; 37: 155.
[33] Kowalchuk C, Kanagasundaram P, Belsham DD, Hahn MK. Antipsychotics differentially regulate insulin, energy sensing, and inflammation pathways in hypothalamic rat neurons. Psychoneuroendocrinology. 2019; 104: 42–48.
[34] Vogt MC, Brüning JC. CNS insulin signaling in the control of energy homeostasis and glucose metabolism - from embryo to old age. Trends in Endocrinology and Metabolism: TEM. 2013; 24: 76–84.
[35] Hahn M, Chintoh A, Giacca A, Xu L, Lam L, Mann S, *et al*. Atypical antipsychotics and effects of muscarinic, serotonergic, dopaminergic and histaminergic receptor binding on insulin secretion in vivo: an animal model. Schizophrenia Research. 2011; 131: 90–95.
[36] Kapur S, Zipursky RB, Remington G. Clinical and theoretical implications of 5-HT2 and D2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. The American

Journal of Psychiatry. 1999; 156: 286–293.
[37] Tramunt B, Smati S, Grandgeorge N, Lenfant F, Arnal J, Montagner A, *et al*. Sex differences in metabolic regulation and diabetes susceptibility. Diabetologia. 2020; 63: 453–461.
[38] Boyda HN, Procyshyn RM, Tse L, Yuen JWY, Honer WG, Barr AM. A comparison of the metabolic side-effects of the second-generation antipsychotic drugs risperidone and paliperidone in animal models. PLoS ONE. 2021; 16: e0246211.
[39] Powell SB. Models of neurodevelopmental abnormalities in schizophrenia. Current Topics in Behavioral Neurosciences. 2010; 4: 435–481.