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Adipocyte Triglyceride Content and Adipogenesis in Aripiprazole Treated Rats

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Abstract: The atypical antipsychotic treatment is associated with weight gain and alteration of glucose and lipid metabolism. The effects of aripiprazole which is a third generation antipsychotic drug associated with reduced weight gain, were investigated on adipose tissue. The triglyceride content of adipose tissue along with adipocyte's lipid droplet size was determined. The experiments were performed using adult, female Wistar rats, divided in 3 groups as follows: Control group (n = 8) -vehicle, aripiprazole 4 mg kg⁻¹ b.wt. (n = 8) and aripiprazole 8 mg kg⁻¹ b.wt. (n = 8). The drugs were administered orally twice daily for 32 days. Samples were taken from perirenal area, triglyceride content of cells was determined using colorimetric enzymatic method. Histological evaluation of the perirenal adipose tissue was performed by morphological characterization of adipocytes. The triglyceride content of adipocytes was significantly lower in the aripiprazole treated groups than in control (p<0.001). The triglyceride level lowering effect was not dose dependent, the difference between the two treated groups was not statistically significant (p>0.05). Evaluating the lipid droplet size distribution, we found significant difference between control and treated groups (p<0.001). The aripiprazole treatment caused a marked decrease in lipid droplet size. The morphological evaluation confirmed an increased presence of multivacuolar fat cells. The decrease in triglyceride content of adipose tissue associated with increased multivacuolar cell presence could suggest that aripiprazole treatment may increase the preadipocyte proliferation.

Key words: Antipsychotic drugs, aripiprazole, weight gain, adipogenesis, triglyceride

INTRODUCTION

Atypical antipsychotics were studied thoroughly in the last decades, owing to the fact that the introduction of this drugs led to the appearance of set of new adverse effect among patients (Haupt, 2006; Heiskanen *et al.*, 2003; Newcomer, 2005; Straker *et al.*, 2005). The treatment-induced weight gain by Atypical Antipsychotics (AAS) can be considered the start-point of a developing metabolic syndrome. The increased Body Mass Index (BMI), especially increased abdominal adiposity is associated with insulin resistance. The decrease of insulin sensitivity, changes in plasma glucose level and the alteration of lipid profile lead to metabolic syndrome in 30-40% of patients (De Hert *et al.*, 2009; Straker *et al.*, 2005). So the most important side effect of the newly introduced drugs is the more significant weight gain compared to conventional drugs, although some representative of the latter group also causes weight gain (Allison *et al.*, 1999).

Based on numerous clinical trials conclusions were drawn regarding the weight gaining potential of AAS, sorting these drugs based on the extent of weight gain. Clozapine and olanzapine are considered to have the greatest potential to induce weight gain; risperidone, quetiapine and zotepine low to moderate potential, while ziprasidone and aripiprazole are considered to have minimal side effects (Newcomer, 2005). In order to explain the underlying differences between these structurally different drugs' side effects, scientists revealed and tested several hypotheses: Receptor affinity differences of drugs may contribute to the weight gain potential, proving that H₁ histamine receptor affinity correlates with weight gain (Kim *et al.*, 2007; Kroeze *et al.*, 2003) but 5-HT_{2C} serotonin receptors were also described as possible site of actions for food intake modulation (Bonhaus *et al.*, 1997; Hartfield *et al.*, 2003) and majority of AAS have high to moderate, respectively moderate to low affinity to these receptors (Abi-Dargham and Laruelle, 2005; Miyamoto *et al.*, 2005).

Neither 5-HT_{2C} serotonin receptor antagonism, nor H₁ histamine receptor antagonism or other central effect through adrenergic or dopamine systems (Reynolds and Kirk, 2010) were capable to fully explain the resulting phenomena, so searching for peripherally located direct sites of action which induce adipose tissue differentiation and proliferation were launched. Evidence was found that clozapine and olanzapine share the same target protein, the Sterol Regulatory Element-binding Protein 1 (SREBP-1) which plays an important role in adipocyte life cycle as transcription factor. Another possibly involved factor is the Peroxisome Proliferator-activated Receptor gamma (PPAR- γ) (Ferno *et al.*, 2009; Yang *et al.*, 2007, 2009). These findings indicate that clozapine and olanzapine beside their central effects have direct peripheral effect on adipose tissue which could explain the marked potency of the two drugs to induce weight gain.

One of the newest compounds, aripiprazole is considered a “third generation” drug, differing from other AAS in its intrinsic activity on some receptors (Keck Jr. and McElroy, 2003; Nasrallah, 2008). It has moderate affinity to H₁ histamine receptors and is a weak partial agonist on 5HT_{2C} serotonin receptor (DeLeon *et al.*, 2004; Shapiro *et al.*, 2003), so it influences slightly the appetite. Although the short-term weight gain of this drug is the least among atypical antipsychotics, clinical studies showed strange results on long-term treatment. In a 26-week study the proportion of patient who gained weight above 7% of baseline body mass was greater than 5%. This proportion increased in a 52-week trial to 30% among patients with initial BMI<23, 19% among patients with BMI between 23-27 and among those with BMI>27 the weight gain rate was smaller, only about 8% of patients gained more than 7% of baseline weight (Kasper *et al.*, 2003). Although aripiprazole showed safer profile than olanzapine in a multicenter, randomized, double blind safety and tolerability study 29% of patients had a significant weight gain which was defined as a $\geq 7\%$ increase from baseline (BMS, 2004). The mechanism of this side effect has not been clarified yet. To explore the peripheral, direct effects of aripiprazole on adipose tissue, the evaluation of biochemical and morphological characteristics of adipocytes was proposed which are relevant parameters regarding adipogenesis.

MATERIALS AND METHODS

Animals: Twenty-four female Wistar rats, 45-55 weeks age, weighing between 270-380 g were provided by the Biobase of University of Medicine and Pharmacy Targu Mures and used for the present study. The animals

were randomly divided in three groups, each group consisted of eight animals (n = 8). For housing standard cages were used with four animals in each. Food and water was available *ad libitum*, the light-dark cycle was 12 h assured by natural light. The temperature and relative humidity of the rooms was 22 \pm 2°C and 3-60%, respectively.

All experimental procedures were approved by the Ethics Committee of the University of Medicine and Pharmacy Targu Mures (No. 27/29.10.2010) and were performed under the European Union's guidelines described in Directive 2010/63/EU.

Study design: In order to evaluate an eventually dose related effect of the orally administered aripiprazole on adipose tissue aripiprazole was administered in two different dosage for 32 days. The experiment was performed on three groups, as follows: One control group (A) Which received vehicle in a similar volume as treated groups; two aripiprazole treated groups: One received a daily dose of 4 mg kg⁻¹ b.wt. (B) And another which received 8 mg kg⁻¹ b.wt. day⁻¹ (C) Weekly changes of body weight during the experiment was followed and evaluated. After the treatment period animals were euthanized with an overdose of anesthetics. Adipose tissue samples were taken from perirenal region, these region being described as the most specific and sensitive to study adipogenesis (Caserta *et al.*, 2001).

Experimental procedures: Aripiprazole, the active substance was provided by Gedeon Richter Romania. Oral solution of aripiprazole with 1 mg mL⁻¹ concentration was prepared using the following excipients (mg mL⁻¹): Glycerol (150), lactic acid (8.47), sodium hydroxide 2.5 N (0.45), propylene glycol (50) and purified water (q.s.) (modified composition of “Aripiprazole oral solution”, Patent no. US 2002/0193438 A1). Usage of antimicrobial preservatives was omitted because the solutions were prepared daily-ex tempore. The drug was administered orally, twice daily (8:00 a.m. and 4:00 p.m.) through intragastric gavage in a volume of 2 mL kg⁻¹ b.wt. for (4 mg kg⁻¹ b.wt.) and 4 mL kg⁻¹ b.wt. for (8 mg kg⁻¹ b.wt.). The control group received vehicle with the above described composition in a volume of 2 mL kg⁻¹ b.wt.

Triglyceride content determination: The extraction and homogenization of triglycerides from perirenal tissue consisted of the following steps: Precisely weight quantity was undergone cell lysis by 1 min ultrasonication in a 10% w/w Tween 20 solution; to ensure the solubilization of triglycerides. Solutions were heated to 80°C, followed by another 1 min of ultrasonication after the cool down at room temperature.

The concentration of the final solution was determined using a commercially available kit for triglyceride quantification (Diagnosticum Rt., Budapest) which contained a reagent solutions and a standard. The composition is: Reagent-Pipe buffer pH = 7.20, p-chlorophenol, Mg²⁺, adenosine-5'-triphosphate (ATP), lipoprotein lipase, glycerol kynase, glycerol phosphate oxidase, peroxidase, 4-aminoantipyrine; standard-glycerol (2.28 mmol L⁻¹). The measurement of absorbance was performed using a Shimadzu UV-1601 UV-Visible Spectrophotometer at 505 nm wavelength and 37°C in a 0.5 cm light path glass cuvette against reagent blank.

Morphological analyzes of the adipose tissue: Sampled tissue were fixed in 10% buffered formalin and embedded in paraffin. Hematoxylin and Eosin (HE) stained sections were prepared from perirenal adipose tissue. Dissection was carried out so that to maximize adipose tissue sampling on sectioning. Microscopic examination was performed in order to verify tissue integrity followed by the digital acquisition of slides. This was achieved using a Zeiss MiraxScan digital slide acquisition system (Carl Zeiss Jena GmbH, Germany), mounted with a Marlin F-146C (Sony ICX267 sensor) digital camera (Allied Vision Technologies GmbH, Germany). The control of the system was assured by MiraxScan software installed on a Fujitsu-Siemens Celsius Workstation.

Morphometric analyses were performed on images captured with Panoramic Viewer (3Dhistech, Budapest), by visual selection and built-in measurement of the multivacuolar cell islets' surface in each section. Cell counting and size measurement was carried out with ImageJ software (Wayne Rasband, National Institute of Health, Bethesda, Maryland, USA) as described by Christine Labno (University of Chicago), with slight modifications in order to obtain the optimal signal-to-noise ratio.

Statistical analysis: The statistical analyses were performed with the trial version of the software GraphPad Prism 5. Every set of data has undergone outlier detection using the Grubbs' test and data which showed unexplainable difference was considered analytical error and was excluded. The decisions to use one-way ANOVA test or Kruskal-Wallis test for the comparison of groups was based on the Gaussian distribution of each data set. Post tests used in each case were: Bonferroni's Multiple Comparison test, with correction method for multiple comparisons and Dunn's Multiple Comparison Test respectively. The results were expressed as means and Standard Deviation (SD) for parametric data and

median with interquartile range for non-parametric data. For all analyses the significance level was considered p value <0.05.

RESULTS

The body weight follow-up showed us that chronic treatment with aripiprazole did not induce statistically significant weight gain in rodents (p>0.05), contrary a slight reduction was observed (Fig. 1). An astounding 50-60 g reduction of body weight was described in the first week.

The triglyceride content of adipose tissue described as a percentage of adipose tissue mass (g%) (Table 1) showed significant difference between the three groups p<0.001. The control group contained 27.3 g% triglyceride while the groups treated with 4 mg kg⁻¹ b.wt. and 8 mg kg⁻¹ b.wt. aripiprazole stored 10.3 g and 12.4 g% triglyceride, respectively. This decrease of triglyceride content is statistically significant between control versus treated groups but it is not dose dependent -insignificant difference between the two dosage (Fig. 2).

Examining the morphological characteristics of the perirenal adipose tissue it was found that aripiprazole treatment dose-dependently modified the lipid accumulation of cells. The surface of each lipid droplet from the stained samples of perirenal tissue was quantified (Fig. 3). The increased number of measured cells-more than twenty thousand in each group-enabled us to detect the significant differences between groups (p<0.0001) (Table 2). Aripiprazole treatment with the dose

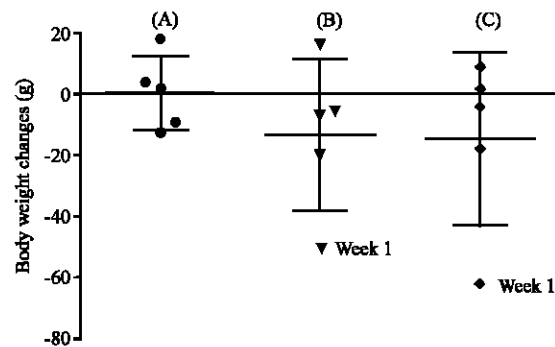


Fig. 1: The weekly change of the animal's body weight. Each plot represents the average body weight gain/reduction of the respective group reported of the previous week. The mean change during the treatment period did not show significant difference between groups (A) Control group (B) Aripiprazole 4 mg kg⁻¹ b.wt. and (C) Aripiprazole 8 mg kg⁻¹ b.wt.

Table 1: Adipose tissue triglyceride content (g%)

No. of animal	Control group (A)		Aripiprazole 4 mg kg ⁻¹ b.wt. (B)		Aripiprazole 8 mg kg ⁻¹ b.wt. (C)	
	Mean	SD	Mean	SD	Mean	SD
1	34.0	4.1	13.5	5.4	15.2	3.4
2	31.5	3.4	15.4	4.1	25.7*	5.3*
3	21.6	2.7	14.7	4.0	13.8	5.1
4	23.6	4.5	9.3	3.0	15.2	12.4
5	24.1	7.4	8.1	4.3	13.4	9.8
6	22.1	2.8	9.0	3.9	6.3	0.1
7	-**	-**	5.9	3.6	12.7	3.0
8	34.4	5.9	6.6	4.8	9.9	2.7
No. of values	7		8		7	
Mean	27.3		10.3		12.4	
SD	5.7		3.7		3.2	
Coefficient of variation	20.8%		35.9%		26.1%	

*Triglyceride content value was excluded based on the outlier Grubbs test result, **The animal died in the first week of the experiment without any identifiable cause

Table 2: Lipid droplets surface size determination and its statistical evaluation

Parameter	Control group (A)	Aripiprazole 4 mg kg ⁻¹ b.wt. (B)	Aripiprazole 8 mg kg ⁻¹ b.wt. (C)
No. of values (N)	79631	51474	20619
Mean (µm ²)	900.3	508.8	1336
Standard Deviation	1347*	1127*	1715*
Minimum (µm ²)	15.04	15.04	15.04
25% Percentile (µm ²)	41.67	36.5	100.5
Median (µm ²)	234**	115**	585**
75% Percentile (µm ²)	1267	366	1994
Maximum (µm ²)	11674	11933	11984
Coefficient of variation (%)	149.60	221.49	128.38
Skewness	2.194	4.164	1.876
Kurtosis	5.790	21.30	3.939

*Does not follow Gaussian distribution, **p<0.05-Kruskall-Wallis test followed by Dunn's multiple comparison test

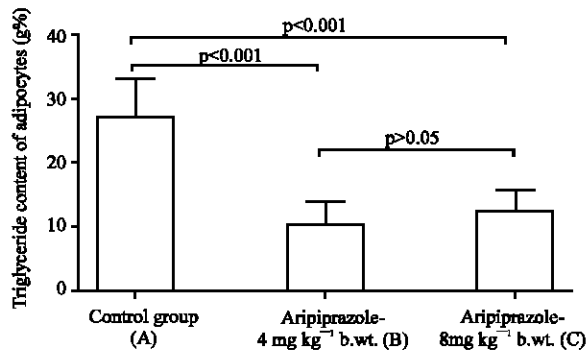


Fig. 2: Triglyceride content of adipocytes with the statistical evaluation of the differences between groups

of 4 mg kg⁻¹ b.wt. decreased the surface of lipid droplets to a median value of 115 µm² compared to the 234 µm² found in control group. An increase to 585 µm² median lipid droplet size was observed in the aripiprazole treated group which received the higher dose (8 mg kg⁻¹ b.wt.). Evident differences are observable between the compositions of different adipose tissues (Fig. 4).

Measuring the presence of multivacuolar cells in the sampled tissue differences were found after aripiprazole

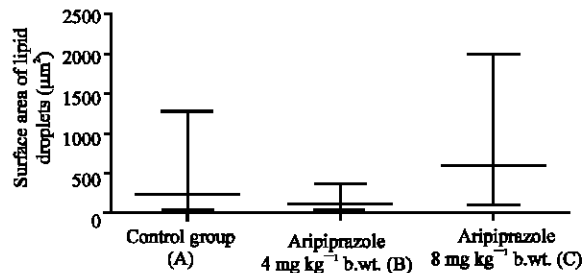


Fig. 3: The surface area of lipid droplets in perirenal adipocytes. The results are expressed as medians±interquartile ranges (25/75%)

treatment. A twofold increase of multivacuolar cell presence of was observed but it was not significant due to high variability (Fig. 5).

DISCUSSION

Atypical antipsychotics cause significant weight gain during long term therapy (Allison *et al.*, 1999) which contributes to the development of metabolic syndrome among schizophrenic patients (De Hert *et al.*, 2009). Kalinichev *et al.* (2005) described the Wistar female rats

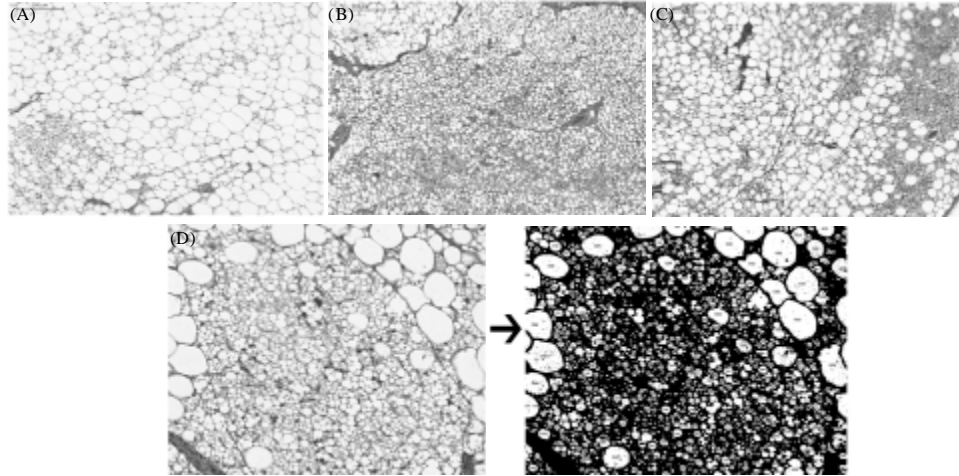


Fig. 4(A-D): Representative images of perirenal adipose tissue from: Control group (A), Aripiprazole 4 mg kg⁻¹ b.wt. (B) Aripiprazole 8 mg kg⁻¹ b.wt. (C) Images were transformed to determine lipid droplet size with ImageJ (D)

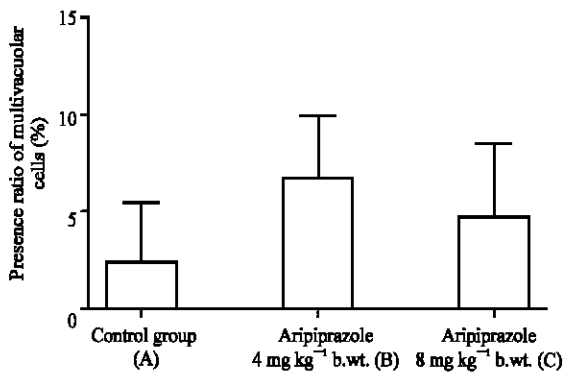


Fig. 5: Multivacuolar cell presence expressed as surface ratio in total examined adipose tissue

as the most sensitive laboratory animal to the weight gain inducing effect of antipsychotics (Kalinichev *et al.*, 2005), especially to aripiprazole which induces significant weight gain after one week. The obtained results show the contrary of this fact. The observed a slight reduction of body weight but without any significant difference between control and treated groups are in accordance with clinical observations (Kane *et al.*, 2002; Kasper *et al.*, 2003; Keck Jr. and McElroy, 2003). It is a widely accepted fact that pharmacokinetic properties, central nervous system penetration or other species related differences put limitations to the extrapolation of data regarding body weight or feeding behavior observed in animal studies to humans. Even if body weight changes are not significant under aripiprazole treatment its influence on adipocyte life cycle could have serious consequences. To the best of our knowledge, this is the first study to evaluate aripiprazole's direct, peripheral effects on adipose tissue.

Adipocytes as they evolve accumulate triglyceride to fulfill their energy storage function. Mature adipose tissue has high triglyceride content, stored in big vacuoles. A significant decrease of the triglyceride content of perirenal adipose tissue was observed after chronic aripiprazole treatment. To thoroughly evaluate the examined effects the size of the vacuoles inside the adipocytes were measured. This parameter is in concordance with adipocyte life cycle progression (Chen and Farese Jr., 2002). A mature, fully evolved adipose tissue contains mainly mature adipocytes with one big vacuole full with triglycerides. Some interesting dose dependent modifications related to vacuole size were found: The smaller dose of aripiprazole enhanced the development of small multivacuolar cells, while vacuolar size was increased using the higher dose of aripiprazole-8 mg kg⁻¹ b.wt. The used optical microscopic evaluation of HE stained adipose tissue has limitations in the differentiation of a preadipocyte from brown adipose tissue (Brooks and Perosio, 2007). However brown adipose tissue can be found in every region of the body its presence is not characteristic in perirenal adipose tissue (Cannon and Nedergaard, 2004; Caserta *et al.*, 2001). So the increased presence of multivacuolar cells suggests some important modifications in adipocytes' life cycle-preadipocyte proliferation or trans-differentiation to brown adipocyte (Frontini and Cinti, 2010; Park *et al.*, 2008). Either of the previously described modifications (preadipocyte proliferation and differentiation or adipose tissue trans-differentiation) could have high impact on aripiprazole usage in future. If it stimulates the preadipocyte proliferation it could determine greater long term weight gain than a simple hyperphagia as side effect.

CONCLUSION

In conclusion, aripiprazole did not caused significant weight gain in healthy Wistar female rats fed with standard chow although it was previously reported by others. Adipose tissue triglyceride content was altered under aripiprazole treatment, both dose (4 and 8 mg kg⁻¹ b.wt.) leading to a significant decrease of triglyceride content in perirenal adipose tissue. Triglycerides accumulated in adipose tissue can reflect the whole body's energy storage level but also characterize the adipocyte's maturity. The morphological inspection of perirenal adipose tissue confirmed an increased presence of immature, multivacuolar adipocytes. Significant difference was shown between control and treated groups regarding the size of the vacuoles. These adipocytes contained smaller vacuoles and were organized in small islets throughout the tissue. The percentage of multivacuolar cells resembling preadipocytes was increased after aripiprazole treatment in perirenal adipose tissue.

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