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RESEARCH

A Novel Insulin Sensitizer Drug Candidate—BGP-15—Can Prevent Metabolic Side Effects of Atypical Antipsychotics

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Abstract Atypical antipsychotic drugs (AAPD) are widely used to treat severe psychiatric disorders, have well documented metabolic side effects such as disturbances in glucose metabolism, insulin resistance and weight gain. It has been shown that BGP-15, a hydroxylamine derivative with insulin sensitizing activity can prevent AAPD provoked fat accumulation in adipocyte cultures, and insulin resistance in animal experiments and in healthy volunteers. The aim of this study was to compare the preventive effect of BGP-15 with conventional oral antidiabetics on metabolic side effects of AAPDs. We found that BGP-15 that does not belong to either conventional insulin sensitizers or oral antidiabetics, is able to counteract insulin resistance and weight gain provoked by antipsychotic agents in rats while rosiglitazone and metformin were not effective in the applied doses. Our results confirm that BGP-15 is a promising new drug candidate to control the metabolic side effects of atypical antipsychotics. Data indicate that this rat model is suitable to analyze the metabolic side effects of AAPDs and the protective mechanism of BGP-15.

Keywords Atypical antipsychotic drugs · Side effects · BGP-15 · Hydroxylamine derivative · Insulin resistance · Weight gain · Hyperinsulinaemic euglycaemic glucose clamp

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Introduction

Drugs termed atypical antipsychotics (AAPD), like clozapine, olanzapine and risperidone represent the second generation of antipsychotic agents and principally used for the treatment of schizophrenia, manic-depressive psychosis and several other psychiatric disorders. AAPDs produce metabolic side effects, especially weight gain, hyperinsulinaemia, type 2 diabetes and dyslipidemia. The exact mechanism responsible for weight gain associated with the use of antipsychotics is not known, although studies have demonstrated that it may result from antagonism of the histaminic and muscarinic receptors and blockade of the 5-HT_{2C} receptors [1], or may directly impair glucose transporter function. [2]. Recently it has been shown that antipsychotics activate SMAD3, a downstream effector of the transforming growth factor beta (TGFβ) pathway but the activation by AAPDs was TGFβ receptor unrelated. The TGFβ pathway and SMAD3 are highly associated with obesity, insulin resistance, and diabetes [3]. The metabolic risks associated with atypical antipsychotics are outlined in the American Diabetes Association-American Psychiatric

Association (ADA-APA) Consensus Guidelines Panel [4]. Moreover studies have shown the prevalence of diabetes and obesity in patients with schizophrenia to be 1.5 to 2 times higher than in unaffected subjects [5]. The metabolic side effects of AAPDs decrease compliance and result in an increased frequency of serious cardiovascular events.

BGP-15 [O-(3-piperidino-2-hydroxy-1-propyl)nicotinic amidoxime dihydrocholride] has been shown to improve metabolic control in various experimental models of diabetes underpinned by an improvement of tissue sensitivity to insulin both in animal models [6] and in insulin-resistant patients [7,8]. Earlier we have shown, that the nonproteotoxic, lipid-interacting BGP-15 capable for heat shock protein (HSP) co-induction in the absence of the production of unfolded proteins. The drug affects those domains of membrane-lipid phase where the thermally or chemically induced perturbation of lipid phase is sensed and transduced into a cellular signal, ultimately leading to an enhanced activation of heat shock protein genes [9]. We have documented that BGP-15 treatment, resulting in increased HSP expression, diminishes the activation of c-jun amino terminal kinase (JNK) and inhibitor of κB kinase (IKK), which are among the major mediators of insulin resistance [10,11]. Previously, we observed that BGP-15 administration prevented olanzapine-induced insulin resistance in healthy volunteers [12]. We have recently reported that BGP-15 could prevent olanzapine-induced reduction in HSP72 protein expression in peripheral monocytes [13]. Furthermore BGP-15 treatment reduced AAPD induced fat accumulation in cultured adipocytes [13].

This series of work was to study the effect of BGP-15 and some currently used antidiabetic drugs on insulin resistance and weight gain provoked by atypical antipsychotic agents in rats.

Materials and Methods

Experimental Animals

The experiments were carried out with adult female Wistar rats weighing 200–220 g, (housed in an animal room 12-hours light/dark periods a day, temperature of 22–25 °C, humidity of 50–70 %). The animals were fed commercial laboratory chow and allowed free access to tap water ad libitum. The treatments began after 1-week acclimatization to the laboratory conditions.

BGP-15 was Provided by N-Gene Inc.

Risperidone + BGP-15 Combination Treatment

The method of Ota [14,15] was used, with modification to study the effect of risperidone on body weight gain. In the experiments, we applied only single daily risperidone treatment in contrast to the twice-daily treatment of the Ota's study. The animals were divided into six groups of ten animals each. Groups were treated either with saline (control group); 0,005 mg/kg risperidone; 0,05 mg/kg risperidone; 20 mg/kg BGP-15; 0,005 mg/kg risperidone +20 mg/kg BGP-15 or 0,05 mg/kg risperidone in combination with 20 mg/kg BGP-15.

Rats were treated subcutaneously with risperidone and orally with BGP-15 once daily for 21 consecutive days. Body weights were measured weekly.

Clozapine + BGP-15 Combination Treatment

The animals were divided into four groups of six animals each. Groups were treated either with saline (control group), 10 mg/kg clozapine alone for 2 months, or 10 mg/kg clozapine (2 months) in combination with 20 mg/kg BGP-15 during the second month of clozapine treatment (1 month) or 20 mg/kg BGP-15 alone for 2 months. Insulin sensitivity was determined by hyperinsulinemic euglycemic glucose clamp.

Olanzapine + BGP-15 Combination Treatment

The animals were divided into eight groups of six animals each. Groups were treated either with saline (control group), 1 mg/kg olanzapine, 10 mg/kg BGP-15, 100 mg/kg metformin, 3 mg/kg rosiglitazone, or 1 mg/kg olanzapine plus 10 mg/kg BGP-15, 1 mg/kg olanzapine + 100 mg/kg metformin or 1 mg/kg olanzapine + 3 mg/kg rosiglitazone for 28 days. The whole body insulin sensitivity, body weight was determined at the end of the 28-day treatment period, body weights were measured weekly.

Hyperinsulinaemic Euglycaemic Glucose Clamp (HEGC)

Whole body insulin sensitivity was determined by hyperinsulinaemic euglycaemic glucose clamping essentially as described [16]. Human regular insulin was infused at a constant rate (5–12 mU/kg/min) via a catheter inserted into one of the jugular veins over 120 min. This insulin infusion rate was adjusted to procedure 100±5 μU/ml in steady state in each species. Blood samples (0.2 ml) were taken from an arterial cannula introduced into one of the external carotid arteries for blood glucose concentration at 10-minutes intervals. Blood glucose concentration was maintained constant (5.5±0.5 mmol/l) by a variable rate of glucose infusion. When blood glucose has stabilized for at least 20 min, we defined this condition as steady state. The glucose infusion rate during steady state was used to characterize insulin sensitivity.

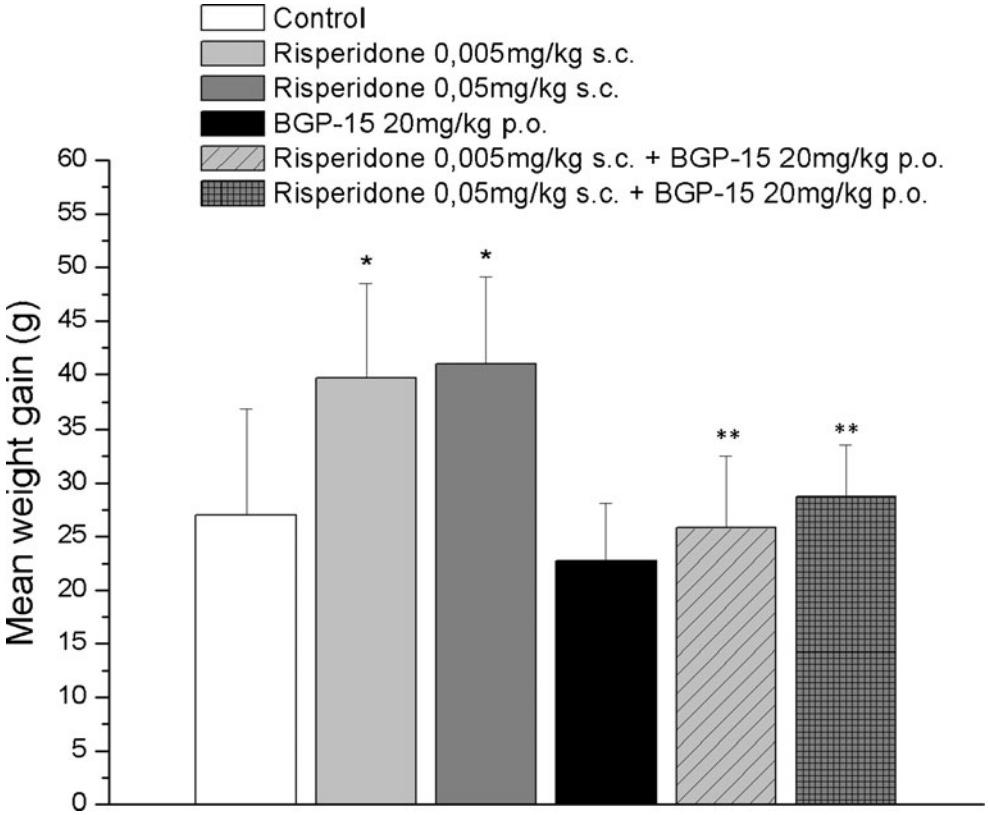

Fig. 1 The effect of BGP-15 on risperidone induced weight gain. The results are expressed as means ± S.D. obtained with 10 animals per group. *Significantly different from the control. ** Significantly different from risperidone treated groups. The data were analyzed with repeated-measures ANOVA followed by Student's *t*-test modified according to Bonferroni's method. Changes were considered statistically significant at P<0.05

Statistics

The results were analyzed with one-way analysis of variance followed by a modified *t*-test for repeated measures according to Bonferroni's method [17]. Changes were considered significant at P<0.05.

Results

The Effect of BGP-15 on Risperidone Induced Weight Gain

In the presented study 21-day risperidone treatment resulted in a significant increase in body weight gain in rat. Our results are in concert with the observations of Ota [14,15]. BGP-15 alone had no significant effect on body weight gain. BGP-15 significantly decreased the rate of body weight gain when it was applied in combination with risperidone (Fig. 1).

The Effect of BGP-15 on Clozapine Induced Insulin Resistance

The aim of this experiment was to evaluate whether BGP-15 can improve insulin sensitivity after a chronic (1 month) clozapine treatment.

Two-month clozapine treatment resulted in significant insulin resistance in female Wistar rats. Glucose infusion rate was by 38 % lower in clozapine treated than in the vehicle treated control animals in hyperinsulinemic euglycemic clamp test. BGP-15 treatment significantly ameliorated the clozapine-induced insulin resistance. Glucose infusion rate was higher in BGP-15 treated than in the control group, but the difference was not statistically significant at P<0,05 level (Table 1).

Effect of BGP-15 on Olanzapine Induced Metabolic Side Effects

Olanzapine at the dose applied induced insulin resistance. The insulin induced glucose utilization was decreased by about 60 %. BGP-15 significantly restored whole body insulin sensitivity in olanzapine-treated animals. The

Table 1 Effect of BGP-15 on glucose infusion rate in rats with established insulin resistance caused by clozapine treatment. *Significantly different from the control, **Significantly different from the clozapine treated group. P<0,05. ANOVA, Bonferroni post hoc test

Treatment groups	N	Mean of glucose infusion rate (mg/kg/min)	s.e.
Control – (Saline)	6	21,63	1,05
Clozapine 10 mg/kg	6	13,53*	0,72
Clozapine 10 mg/kg + BGP-15 20 mg/kg	6	18,32**	0,93
BGP-15 20 mg/kg	6	22,78	1,27

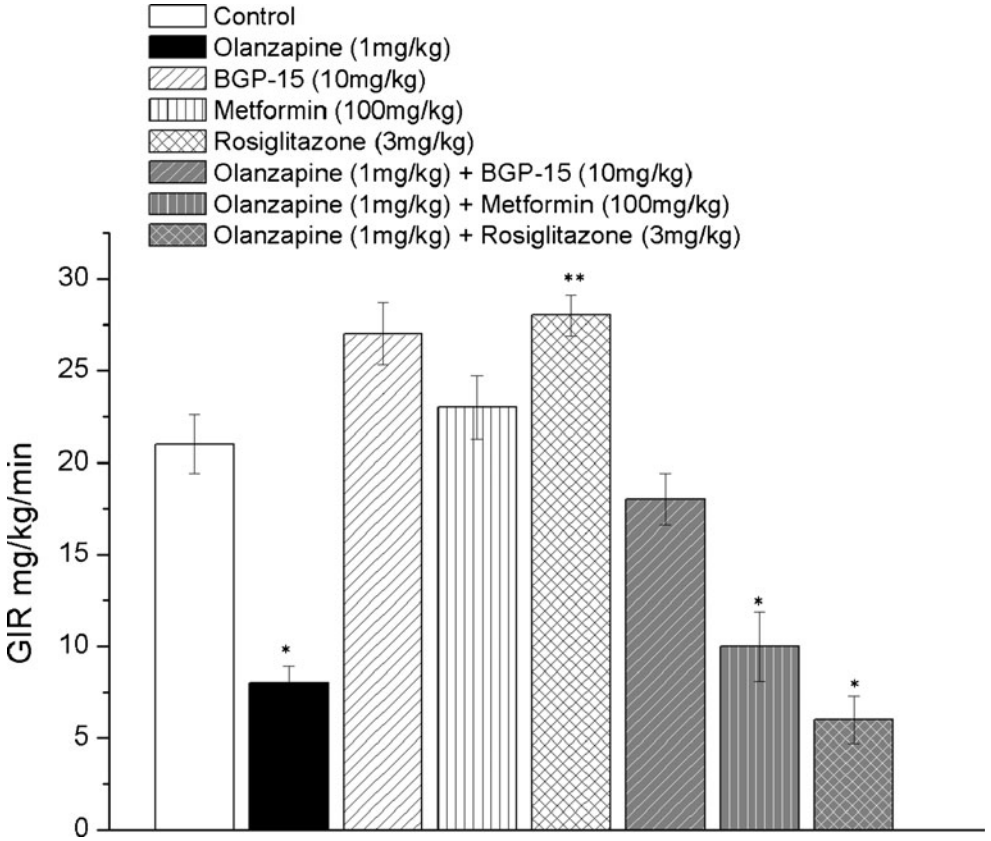

Fig. 2 The effect of BGP-15 compared with oral antidiabetics on olanzapine provoked insulin resistance. *Significantly different from the control. **Significantly improved insulin sensitivity compare with control group. ***Significantly different from olanzapine treated groups. The results expressed as means ± S.D. were analyzed with one-way analysis of variance followed by a modified *t*-test for repeated measures according to Bonferroni's method [17]. Changes were considered significant at $P<0.05$.

hydroxylamine derivative by itself did not influence insulin sensitivity in healthy animals (Fig. 2). The data also show that BGP-15 inhibits weight gain associated with subchronic administration of olanzapine (Fig. 3). Nevertheless, neither metformin nor rosiglitazone produced any significant effect in the applied doses in insulin sensitivity or prevented weight gain provoked by olanzapine (Fig. 2; 3).

Discussion

The series of experiments described above demonstrate that BGP-15 abolishes the development of olanzapine-induced insulin resistance under conditions, at which conventional insulin sensitizers such as metformin and rosiglitazone in the applied doses were not effective.

Although it is well known that the metabolic side effects of AAPD appears also in rodents including rats and mice, only few study analyzed the effect of the existing antidiabetic agents on the metabolic side effects of AAPD in animal models [18]. In a previous study, Arulmozhi et al. observed that rosiglitazone exhibited beneficial glucose and triglyceride lowering effects in mice treated over a period of 7-days [19].

We evaluated the effect of rosiglitazone, metformin and a new insulin sensitizer candidate BGP-15 on weight gain and insulin resistance provoked by subchronic olanzapine treatment (Fig. 2; 3). Moreover the results of this study indicate that BGP-15 is also efficient in existing insulin resistance caused by antipsychotic drugs. BGP-15 treatment can reverse insulin resistance even after extended antipsychotic drug therapy (Table 1).

In patients with severe mental illness, obesity can be attributed to an unhealthy lifestyle, personal genetic profile, and to a great extend antipsychotic drug therapy. Since the introduction of the AAPDs, a 0.7 % per year increase in incidence of type 2 diabetes has been seen in patients compared with the general population [20]. Insulin resistance, type 2 diabetes mellitus, obesity, coronary heart disease, and hypertension at least in part due to AAPD medication can significantly contribute to an approximately 20 % shorter life expectancy than in general population [21].

Several conventional antidiabetics have been tested to reduce or prevent the metabolic side effects of antipsychotic

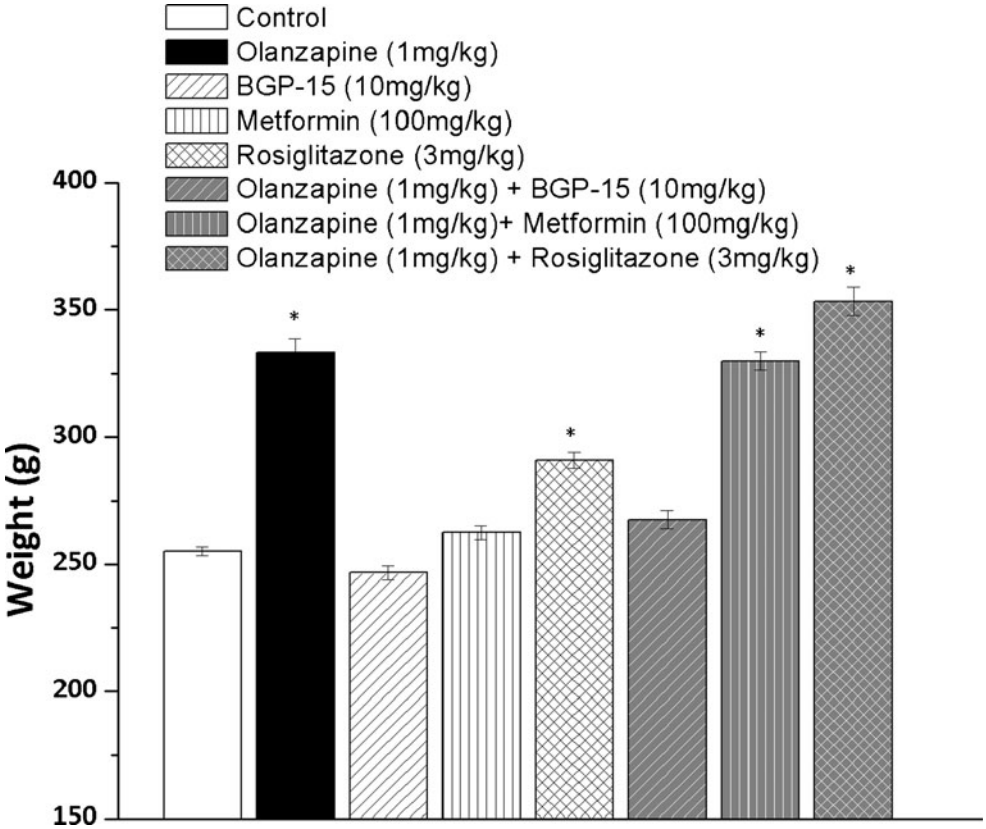

Fig. 3 The effect of BGP-15 compared with oral antidiabetics on olanzapine induced weight gain. *Significantly different from the control. The results expressed as means ± S.D. were analyzed with one-way analysis of variance followed by a modified *t*-test for repeated measures according to Bonferroni's method [17] Changes were considered significant at P<0,05

drugs. The preventive effect of metformin was controversial in clinical trials. Ren-Rong Wu et al. observed that metformin attenuated the antipsychotic-induced weight gain in drug-naive young patients [22]. On contrary, Trino Baptista et al. have found that in a 14-week long clinical trial, metformin did not produce any significant preventive effect on AAPD-induced metabolic abnormalities [23]. Rosiglitazone did not improve insulin sensitivity in combination with clozapine [24] and could not prevent olanzapine induced weight gain [25].

Moreover, in diabetic patients, metformin did not prevent cardiovascular complications, and rosiglitazone was associated with a significantly increased risk of heart attack (odds ratio=1.43, (95 % confidence interval, 1.03 to 1.98; P= 0,03), and an even higher risk of death from all cardiovascular diseases (odds ratio=1.64) [26]. Furthermore, our previous results indicate that besides preventing insulin resistance, BGP-15 may have additional cardiovascular protective activity i.e. it prevented ischaemia/reperfusion-induced heart injury, restored vascular responsiveness in insulin resistance [8,27,28]. Recently it has been also demonstrated that BGP-15 confers protection against rapid pacing-induced atrial fibrillation, at least in a Drosophyla melanogaster model of cardiac arrhythmias [8,29].

We conclude that BGP-15 may be considered as a promising new drug candidate for pharmacological interventions to prevent metabolic side effects of AAPD treatment. Therefore, the drug candidate may serve as a pharmacological tool to increase the compliance during antipsychotic therapy and, as expected, may also reduce the occurrence of cardiovascular complications in patients suffering from psychiatric diseases treated with 2nd generation neuroleptics. Overall, this may be of importance in increasing life expectancy of psychiatric patients.

References

1. Gardner DM, Baldessarini RJ, Waraich P (2005) Modern antipsychotic drugs: a critical overview. CMAJ 172:1703–1711
2. Dwyer DS, Donohoe D (2003) Induction of hyperglycemia in mice with atypical antipsychotic drugs that inhibit glucose uptake. Pharmacol Biochem Behav 75:255–260
3. Cohen T, Sundaresh S, Levine F (2012) Antipsychotics activate the TGFβ pathway effector SMAD3. Molecular Psychiatry. doi:10.1038/mp.2011.186
4. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity (2004) Consensus development

conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry 65:267–272
5. De Hert M, van Eyck D, De Nayer A (2006) Metabolic abnormalities associated with second generation antipsychotics: fact or fiction? Development of guidelines for screening and monitoring. Int Clin Psychopharmacol 21(suppl 2):S11–5
6. Kürthy M, Mogyorósi T, Nagy K, Kukorelli T, Jednákovits A, Tálosi L et al (2002) Effect of BRX-220 against peripheral neuropathy and insulin resistance in diabetic rat models. Ann N Y Acad Sci 967:482–9
7. Literáti-Nagy B, Kulcsár E, Literáti-Nagy Z, Buday B, Pétrfai E, Horváth T, Tory K, Kolonics A, Fleming A, Mandl J, Korányi L (2009) Improvement of insulin sensitivity by a novel drug, BGP-15, in insulin-resistant patients: a proof of concept randomized double-blind clinical trial. Horm Metab Res 41:374–380
8. Tim Crul, Noemi Toth, Stefano Piotto, Peter Literati-Nagy, Kalman Tory, Pierre Haldimann, Bernadett Kalmar, Linda Greensmith, Zsolt Torok, Gabor Balogh, Imre Gombos, Federica Campana, Simona Concilio, Ferenc Gallyas, Gabor Nagy, Zoltan Berente, Burcin Gungor, Maria Peter, Attila Glatz, Akos Hunya, Zsuzsanna Literati-Nagy, Laszlo Vigh Jr., Femke Hoogstra-Berends, André Heeres, Irma Kuipers, Lizette Loen, Jean-Paul Seerden, Deli Zhang, Roelien A M Meijering, Robert H Henning, Bianca JJM Brundel, Harm H Kampinga, Laszlo Koranyi, Zoltan Szilvassy, Jozsef Mandl, Balazs Sumegi, Mark A Febbraio, Ibolya Horvath, Philip L Hooper, Laszlo Vigh (2012) Hydroximic acid derivatives: pleiotrophic HSP coinducers restoring homeostasis and robustness. Curr. Phar. Des (in press).
9. Gombos I, Crul T, Piotto S, Güngör B, Török Z, Balogh G, Péter M, Slotte PJ, Pilbat AN, Hunya A, Tóth N, Literati-Nagy Z, Vigh L Jr, Glatz A, Brameshuber M, Schütz GJ, Hevener A, Febbraio MA, Horváth I, Vígh L (2011) Membrane-lipid therapy in operation: the HSP co-inducer BGP-15 activates stress signal transduction pathways by remodeling plasma membrane rafts. PLoS One 6 (12):e28818
10. Hargitai J, Lewis H, Boros I, Rácz T, Fiser A, Kurucz I, Benjamin I, Vígh L, Pénzes Z, Csermely P, Latchman DS (2003) Bimoclomol, a heat shock protein co-inducer, acts by the prolonged activation of heat shock factor-1. Biochem Biophys Res Commun 307(3):689–95
11. Chung J, Nguyen AK, Henstridge DC, Holmes AG, Chan MH, Mesa JL, Lancaster GI, Southgate RJ, Bruce CR, Duffy SJ, Horvath I, Mestril R, Watt MJ, Hooper PL, Kingwell BA, Vigh L, Hevener A, Febbraio MA (2008) HSP72 protects against obesity-induced insulin resistance. Proc Natl Acad Sci USA 105:1739–1744
12. Literáti-Nagy B, Péterfai E, Kulcsár E, Literáti-Nagy Z, Buday B, Tory K, Mandl J, Sümegi B, Fleming A, Roth J, Korányi L (2010) Beneficial effect of the insulin sensitizer (HSP co-inducer) BGP-15 on olanzapine-induced metabolic disorders. Brain Res Bull 83:340–344
13. Literáti-Nagy Z, Tory K, Literáti-Nagy B, Kolonics A, Török Z, Gombos I, Balogh G, Vígh L Jr, Horváth I, Mandl J, Sümegi B, Hooper PL, Vígh L (2012) The HSP co-inducer BGP-15 can prevent the metabolic side effects of the atypical antipsychotics. Cell Stress Chaperon. doi:10.1007/s12192-012-0327-5
14. Ota M, Mori K, Nakashima A, Kaneko YS, Takahashi H, Ota A (2005) Resistance to excessive bodyweight gain in risperidone-injected rats. Clin Exp Pharmacol Physiol 32:279–87
15. Ota M, Mori K, Nakashima A, Kaneko YS, Fujiwara K, Itoh M, Nagasaka A, Ota A (2003) Peripheral injection of risperidone, an atypical antipsychotic, alters the bodyweight gain of rats. Clin Exp Pharmacol Physiol 30:513–4
16. Porszasz R, Legvari G, Pataki T, Szilvassy J, Nemeth J, Kovacs P, Paragh G, Szolcsanyi J, Szilvassy Z (2002) Sensory nitrergic nature of the hepatic insulin sensitizing substance mechanism in conscious rabbits. Eur J Pharmacol 17(1–3):211–2, 17
17. Wallenstein S, Zucker CL, Fleiss JL (1980) Some statistical methods useful in circulation research. Circ Res 47(1):1–9
18. Cope MB, Nagy TR, Fernández JR, Geary N, Casey DE, Allison DB (2005) Antipsychotic drug-induced weight gain: development of an animal model. Int J Obes 29(6):607–614
19. Arulmozhi DK, Dwyer DS, Bodhankar SL (2006) Antipsychotic induced metabolic abnormalities: an interaction study with various PPAR modulators in mice. Life Sci 79(19):1865–72
20. Panariello F, De Luca V, de Bartolomeis A (2011) Weight Gain, Schizophrenia and Antipsychotics: New Findings from Animal Model and Pharmacogenomic Studies. Schizophrenia Research and Treatment. doi:10.1155/2011/459284
21. Basu A, Meltzer HY (2006) Differential trends in prevalence of diabetes and unrelated general medical illness for schizophrenia patients before and after the atypical antipsychotic era. Schizophr Res 8:99
22. Wu R-R, Zhao J-P, Guo X-F, He Y-Q, Fang M-S, Guo W-B, Chen J-D, Li L-H (2008) Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain. A randomized controlled trial. JAMA 299:185
23. Baptista T, Rangel N, Fernández V, Carrizo E, Fakih Yamily El, Uzcátegui E, Galeazzi T, Gutiérrez MA, Servigna M, Dávila A, Uzcátegui M, Serrano A, Connell L, Beaulieu S, de Baptista EA (2006) Metformin for prevention of weight gain and insulin resistance with olanzapine: A double-blind placebo-controlled trial. Can J Psychiatry 51:192
24. Henderson DC, Fan X, Sharma B, Copeland PM, Borba CP, Boxill R, Freudenreich O, Cather C, Eden Evins A, Goff DC (2009) A double-blind, placebo-controlled trial of rosiglitazone for clozapine-induced glucose metabolism impairment in patients with schizophrenia. Acta Psychiatr Scand 119(6):457–65
25. Baptista T, Rangel N, El Fakih Y, Uzcátegui E, Galeazzi T, Beaulieu S, Araujo de Baptista E (2009) Rosiglitazone in the assistance of metabolic control during olanzapine administration in schizophrenia: a pilot double-blind, placebo-controlled, 12-week trial. Pharmacopsychiatry 42(1):14–9
26. Wolski K, Steven E (2007) Nissen, Kathy Wolski (2007) Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. N Engl J Med 356:2457–2471
27. Halmosi R, Berente Z, Osz E, Toth K, Literati-Nagy P, Sumegi B (2001) Effect of poly(ADP-ribose) polymerase inhibitors on the ischemia-reperfusion-induced oxidative cell damage and mitochondrial metabolism in Langendorff heart perfusion system. Mol Pharmacol 59:1497–505
28. Szabados E, Literati-Nagy P, Farkas B, Sumegi B (2000) BGP-15, a nicotinic amidoxime derivate protecting heart from ischemia reperfusion injury through modulation of poly(ADP-ribose) polymerase. Biochem Pharmacol 59:937–45
29. Zhang D, Ke L, Mackovicova K, Van Der Want JJ, Sibon OC et al (2011) Effects of different small HSPB members on contractile dysfunction and structural changes in a Drosophila melanogaster model for atrial Fibrillation. J Mol Cell Cardiol 51:381–389