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ORIGINAL ARTICLE

The atypical antipsychotics quetiapine, risperidone and ziprasidone do not increase insulin release in vitro

Kristina Melkersson[a,b*] & Eva Jansson [b]

[a] Sollentuna Psychiatric Polyclinic and
[b] Department of Molecular Medicine, Karolinska Institute, Stockholm, Sweden.

Correspondence to: Kristina Melkersson, MD
Sollentuna Psychiatric Polyclinic
Nytorpsvägen 10
SE-191 35 Sollentuna, SWEDEN
TEL: +46-8-58730405; FAX: +46-8-351318
EMAIL: Kristina.Melkersson@cns.ki.se

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Abstract

OBJECTIVES: In the light of the recent finding that the atypical antipsychotics clozapine and olanzapine have a stimulatory effect on basal insulin release in vitro, the influence on insulin release of three other atypical agents; quetiapine, risperidone and ziprasidone, was examined.
METHODS: The effect of each atypical antipsychotic in a concentration of 10^{-6} M was investigated on both basal and glucose-stimulated insulin release from isolated rat pancreatic islets.
RESULTS: No difference in effect on insulin release was found for any of the three atypical antipsychotic substances compared to controls without antipsychotics, either in basal or in glucose-stimulated insulin release.
CONCLUSION: This study demonstrates that the main compounds of quetiapine, risperidone and ziprasidone do not increase insulin release from isolated pancreatic islets, which stands in clear contrast to what has been found previously for clozapine and olanzapine. Thus, atypical antipsychotics seem to differ in their effect on insulin release in vitro.

Introduction

Adverse metabolic effects, such as weight gain, diabetes mellitus and lipid abnormalities, have increasingly been recognized with the use of the newer, so-called atypical antipsychotic drugs. However, these agents may differ in their risk to affect weight, glucose-insulin homeostasis and lipid metabolism; clozapine and olanzapine appear to have the highest propensity to induce weight gain, diabetes and lipid abnormalities, quetiapine and risperidone intermediary, and ziprasidone the least propensity [1,7,24,17]. Given that insulin is a hormone that is involved in both the regulation of body weight, as well as in glucose regulation and lipid metabolism [19,25], it is worth while studying the potential influence of atypical antipsychotics on pancreatic insulin secretion, and also to compare these agents in this regard.

In in vitro studies, we have recently demonstrated that the atypical antipsychotics clozapine and olanzapine have a stimulatory effect on basal insulin release from isolated pancreatic islets and INS-1 cells [15,16], when conversely, conventional antipsychotics earlier have been shown to inhibit glucose-stimulated insulin release in vitro [2,5,6,9,18,10,22,15]. Accordingly, in clin-

ical studies, treatment with clozapine or olanzapine has been associated with elevated insulin levels and insulin resistance, whereas insulin levels appeared not to be appreciably affected by conventional agents [26,13,14].

The aim of the present study was to continue examining the influence of atypical antipsychotics on insulin release in vitro. We investigated the effect of an additional three atypical agents; quetiapine, risperidone and ziprasidone, on both basal and glucose-stimulated insulin release from isolated rat pancreatic islets.

Materials and Methods

Materials

D(+)Glucose was obtained from BDH Laboratories Supplies (Poole, UK), collagenase A from Roche Diagnostics (Penzberg, Germany), HEPES and histopaque 1119 and 1077 from Sigma (St. Louis, MO, USA), and RPMI 1640 medium and HBSS from the National Veterinary Institute (Uppsala, Sweden). All other chemicals were from either Life Technologies (Paisley, Scotland) or Merck (Darmstadt, Germany).

Isolation and culture of rat pancreatic islets

The study was approved by the ethical committee for research on animals. Pancreata from 3 months old male Wistar rats weighing 330–350 g (B&K Universal, Sollentuna, Sweden) were used. Rats were killed by decapitation, and pancreatic islets were isolated by means of a minor modification of a previously described method [23]. In brief, a catheter was inserted into the common bile duct near to the hilus of the liver, and 7 ml collagenase solution (collagenase type A; 0.9 mg/ml in HBSS was injected into the pancreatic duct system in a retrograde way. Each inflated pancreas was then removed, cleaned of the fat tissue, and incubated in 3 ml collagenase solution at 37 °C for 24 min. After incubation, the pancreata were cut into small pieces (3–4 mm in size), gently syringed several times through a 14 FG needle, washed 3 times in HBSS, and passed through a strainer of approximately 500 μm pore size. Thereafter, islets were isolated from the exocrine pancreatic tissue by centrifugation on a histopaque gradient (800 x g; 20 min). The islets were then cultured overnight at 37 °C in RPMI 1640 supplemented with fetal calf serum (10%), glucose (11 mM), glutamine (2 mM), penicillin (100 IU/ml) and streptomycin (100 μg/ml).

Insulin release

For measurement of insulin release, static incubations were used. Islets were preincubated for 30 min at 37 °C in Krebs-Ringer Bicarbonate (KRB) buffer (pH 7.4) containing in mM: 115 NaCl, 4.7 KCl, 2.56 $CaCl_2$, 1.2 KH_2PO_4, 1.2 $MgSO_4$, 20 $NaHCO_3$ and 10 HEPES, supplemented with 2 mg/ml bovine serum albumin and 3.3 mM glucose. Batches of three islets were then transferred to tubes (in triplicate, n=3), containing 300 μl of KRB buffer with 3.3 or 16.7 mM glucose and the respective antipsychotic substance or no antipsychotic, and incubated for either 1 or 4 h at 37 °C during mild agitation. The incubation was stopped by chilling the samples in ice-water. After centrifugation (200 x g; 1 min), the supernatants were collected and stored at –20 °C until assay.

Antipsychotic substances

Three pure atypical antipsychotic substances: quetiapine (AstraZeneca, UK), risperidone (Janssen Pharmaceutica, Belgium) and ziprasidone (Pfizer, USA), were tested in the concentration of 10^{-6} M and compared to controls without antipsychotics. The substances and the controls were investigated after 1 and 4 h of incubation with the islets, both during basal (i.e. 3.3 mM glucose) and glucose-stimulated (i.e. 16.7 mM glucose) insulin release. In all, four complete experiments were carried out.

Radioimmunoassay

Rat insulin was measured by a radioimmunoassay method, using antibodies against porcine insulin, and charcoal addition to separate bound and free insulin [8]. ^{125}I-labeled porcine insulin was used as tracer and rat insulin as standard (Novo, Bagvaerd, Denmark). The intra- and interassay coefficients of variation were both 2.6%.

Expression of data and statistical analysis

Data are expressed as median with 25th and 75th percentiles. Insulin concentrations in medium from batches treated with antipsychotic substances were calculated as % of the median in control batches. As the data were not normally distributed, the Mann-Whitney rank sum test was performed to evaluate the effect of each antipsychotic substance compared to controls. A P-value of less than 0.05 was considered statistically significant. All calculations were made with the statistical programme Statistica for Windows (Statsoft, Tulsa, OK, USA).

Results

Insulin release in controls

In the controls, the glucose-stimulated insulin release was significantly higher compared to the basal release both after 1 and 4 h of incubation, medians (25th and 75th percentiles) being 731 (523–1497) versus 438 (308–554) mU/L (P= 0.02), and 881 (645–2222) versus 557 (211–902) mU/L (P=0.04), respectively, confirming that the islets used retained an appropriate insulin-secreting responsiveness to glucose.

Insulin release in the presence of antipsychotics

No difference in effect on insulin release was found for any of the three atypical antipsychotic substances (10^{-6}) compared to the control after 1 and 4 h of incubation, either in basal or in glucose-stimulated insulin release (Table 1).

Table 1. Insulin release in % of control, described as median (25th and 75th percentiles). Results are based on four experiments with n=3 in each experiment.

Antipsychotic substances	1 h of incubation		4 h of incubation	
	3.3 mM glucose	16.7 mM glucose	3.3 mM glucose	16.7 mM glucose
Quetiapine	104† (77–115)	105† (78–131)	102† (71–135)	105† (92–128)
Risperidone	97† (88–115)	92† (79–113)	107† (92–120)	93† (73–137)
Ziprasidone	92† (62–119)	110† (66–140)	99† (66–143)	109† (81–153)

† Non-significantly different to controls without antipsychotics

Discussion

The present finding that the atypical antipsychotics quetiapine, risperidone and ziprasidone had no significant effect on insulin release in vitro stands in clear contrast to our previous results showing increased basal insulin release in the presence of both atypical agents clozapine and olanzapine [15,16]. This discrepancy was found, despite the atypical agents in the present and previous studies were tested in the same concentration [15,16]. Nevertheless, taken together, these results point to atypical antipsychotics probably differing in their effect on insulin release in vitro.

Even if atypical antipsychotics belong to one group of antipsychotics, they are in several aspects heterogeneous compounds which bind in various degrees to different types of cell-surface receptors [11,21,3]. Therefore, it is not surprising that these agents may differ in effect on insulin release. However, the exact mechanism(s) underlying atypical agents´ action on pancreatic insulin release is/ are still poorly understood.

Interestingly, the finding in this study that quetiapine, risperidone and ziprasidone do not increase insulin release in vitro is in line with results in clinical studies reporting that these three agents have intermediary, or least propensity, among atypical antipsychotics to induce weight gain, diabetes and lipid abnormalities [1,7,24,17]. In contrast, clozapine and olanzapine, which have been shown to increase basal insulin release in vitro [15,16], have also been found to have the highest potential among the atypicals to induce weight gain, diabetes and lipid abnormalities [1,7,24,17]. Thus, this difference in effect on pancreatic insulin release between atypical antipsychotics, at least in part, may explain the different risks of adverse metabolic effects found among these agents.

In the present study, the main compounds of quetiapine, risperidone and ziprasidone have been tested. It can however, not be excluded that metabolites of these three agents [12,20,4] have an effect on insulin release, something that not have been evaluated in this study.

In conclusion, the present study demonstrates that the main compounds of quetiapine, risperidone and ziprasidone do not increase insulin release from isolated pancreatic islets, which stands in clear contrast to what has been found previously for clozapine and olanzapine. Thus, atypical antipsychotics seem to differ in their effect on insulin release in vitro.

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