Involvement of potassium channels in hypoglycemic effect of sertraline

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Effect of 21 days administration of sertraline (30 mg/kg, po) in streptozotocin (55 mg/kg, ip) induced diabetic and non-diabetic rats produced hypoglycemia in diabetic and non-diabetic rats. Pinacidil (1mg/kg, po), when co-administered with sertraline or glimepiride antagonized the decrease in glucose levels in diabetic rats. Pinacidil (10⁻⁶-10⁻³ M) produced dose dependent relaxation (EC₅₀ -1.58×10⁻⁵ M). Neither sertraline nor glimepiride had any effect on the resting tension of ileum preparation. Both sertraline and glimepiride antagonized competitively the pinacidil-induced relaxation. The pA₂ values of sertraline and glimepiride reversal of pinacidil-induced relaxation were 5.5 and 6.2 respectively. These studies suggest the involvement of K⁺ channels in hypoglycemic effects of sertraline.

Keywords: Diabetes mellitus, Glimepiride, Pinacidil, Potassium channels, Sertraline

Diabetic patients have a 20% higher risk of depression than the general population. Treatment with antidepressants can interfere with blood glucose levels directly or by interacting with hypoglycemic agents. Clinical studies indicate that selective serotonin reuptake inhibitors (SSRIs) are better antidepressants for diabetic patients as compared to tricyclic antidepressants. However, preclinical trials have demonstrated that not all SSRIs reduce plasma glucose levels. For instance, fluoxetine and sertraline, two of the most widely used antidepressants, have been reported to produce opposite effects on glycemic levels. Fluoxetine increases and sertraline decreases glucose levels in diabetic and non-diabetic rats. However, a case of hyperglycemia case due to sertraline has been reported.

Extensive experimental studies indicate a role of 5-HT in glucose regulation. The activation of central 5-HT₁A, 5-HT₂A and 5-HT₂B/2C receptors elevates plasma glucose levels in rats. But the exact picture of 5-HT and/or noradrenaline in SSRIs producing hyperglycemia is not clear.

K⁺ channel blockers promote insulin secretion from pancreatic β-cells whereas K⁺ channel openers have little or no effect on insulin release. Although there are reports indicating a major role of insulin in hypoglycemia associated with sertraline, no precise mechanism has been established. To gain insight into the mechanism by which sertraline produces hypo/hyperglycemia, both in vivo and in vitro studies have been undertaken for better understanding the role of smooth muscle K⁺ channels in altering the glycemic effects in rats.

Materials and Methods

Animals and treatment—Wistar Albino rats of either sex weighing 150-200 g were obtained from the Central Animal House of Jamia Hamdard and housed in polypropylene cages under controlled temperature (27±2°C) and natural light/dark cycle. They were fed with standard laboratory pellets. Food and water were provided ad libitum. The study was conducted as per the guidelines of “Committee for the Purpose of Control and Supervision of Experiments on Animals” (CPCSEA), Ministry of Social Justice and Empowerment, Government of India, New Delhi.

In vivo study—Healthy rats were made diabetic by ip injection of streptozotocin (STZ, 55 mg/kg, Sigma USA). Serum glucose levels were measured 7 days after the injection and animals showing hyperglycemia were selected as diabetic rats. They were randomly divided into 2 subgroups: treated with sertraline (30 mg/kg, Ranbaxy India Ltd), glimepiride (10 mg/kg, Ranbaxy India Ltd) and/or pinacidil (1 mg/kg, Leo Pharmaceuticals, Denmark) by oral route for another 3 weeks. The treatment was started from the 8th day of injection of STZ and continued up to 3 weeks. At the end of the treatment, rats were fasted for 12 hr, blood samples were collected from the tail.
vein and serum was separated. Serum glucose levels were estimated by glucose oxidase peroxidase methods using GOD/POD Kits (Span Diagnostics, India).

**In vitro study**—Segments of terminal ileum (1-1.5 cm long) were removed from the rats. The tissues were suspended in 50 ml inner organ baths containing Tyrode solution, which was bubbled with air and maintained at 37°C. Responses to the drugs were recorded on a drum using an isotonic frontal writing lever, which exerted a 500 mg tension on the tissue that gave 8-10 fold magnification at the responses. The tissue was allowed to equilibrate for 30 min. During this time, the bathing solution was changed every 10 min.

In the first series of experiments, after 30 min stabilization, the smooth muscle was contracted by 80 µM KCl and the responses were allowed to reach a plateau. This was obtained within 10-15 min after the addition of KCl. Pinacidil (10⁻⁶-10⁻³ M) was then added in a cumulative manner. Sufficient time was allowed before the next dose was added. On complete relaxation, the tissue was washed every 5 min and the baseline was restored. Subsequently, the tissue was contracted once again with 80 µM KCl and at plateau, glimepiride (10⁻⁶-10⁻⁴ M) or sertraline (10⁻⁶-10⁻⁴ M) were added and allowed to equilibrate for 10 min. After 10 min, the pinacidil (10⁻⁶-10⁻³ M) was added in a cumulative manner and the relaxation was recorded.

**Statistical analysis**—All values were expressed as mean± SEM. The statistical analysis was performed using One-Way Analysis of Variance followed by Dunnett’s Test. *P<0.05 were considered statistically significant.

**Results**
Sertraline (30 mg/kg) and glimepiride (10 mg/kg) reduced blood glucose levels in non-diabetic and STZ induced diabetic rats (Table 1). Sertraline as well as glimepiride induced decrease in glucose levels was antagonized when pinacidil was co-administered with either of them (Table 1). Addition of pinacidil (10⁻⁶-10⁻³ M) inhibited contractions induced by 80 µM KCl in a concentration dependent manner. The EC₅₀ for pinacidil-induced relaxation in this tissue was determined to be 1.58×10⁻⁵ M.

Addition of sertraline (10⁻⁶-10⁻⁴ M) or glimepiride (10⁻⁶-10⁻³ M) to KCl-contracted ileum did not produce any change in the tension. However, both produced rightward shift of the dose-response curve of pinacidil in a concentration-dependent manner (Fig. 1). The pA₂ values for sertraline and glimepiride reversal of pinacidil relaxation were 5.5 and 6.2, respectively.

**Discussion**
Sertraline (30 mg/kg, po) when given to diabetic rats for 21 days reduced the blood glucose levels significantly. The present results are in agreement with other studies reporting hypoglycemic effects of sertraline¹,³,⁶. Such effects are related to increased insulin output, decreased gluconeogenesis and increased insulin receptor sensitivity⁶. Reports also suggest that sertraline increases glucose stimulated insulin secretion without any change in peripheral insulin sensitivity³.

It is well known that the K⁺ channels are an integral tool in insulin release from pancreatic β-cells upon glucose stimulus. The closure of ATP sensitive K⁺ channels with subsequent depolarization of the cell causes the activation of voltage dependent Ca²⁺ channels followed by increased influx of Ca²⁺ leading to increased insulin release⁷.

Glimepiride and other sulphonyl ureas increase insulin levels by closing the K⁺ channels⁸.

Prior evidence also exist that reports that K⁺ channel blockade enhance the neurotransmitter release by prolonging the presynaptic action potential leading to increased in Ca²⁺ influx⁸. The Ca²⁺ dependent 5-HT synthesis and release is also potentiated through stimulating the 5-HT presynaptic autoreceptors by decreasing K⁺ conductance⁹.

As reported, hypoglycemic effect of sertraline is also associated with increased insulin concentration. On the basis of the present results, it can be concluded that increase in insulin levels producing

**Table 1**—Effects of STZ, sertraline, pinacidil and glimepiride on blood glucose levels in rats
Values are mean± SE from 6 animals in each group

<table>
<thead>
<tr>
<th>Treatment and dose (mg/kg)</th>
<th>Blood glucose level (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control (saline 1ml/kg body wt)</td>
<td>102.66±6.49</td>
</tr>
<tr>
<td>STZ (55)+ Sertraline (30)+ Pinacidil (1)</td>
<td>392.8±15.7*</td>
</tr>
<tr>
<td>STZ (55)+ Sertraline (30)</td>
<td>299.7±15.91*</td>
</tr>
<tr>
<td>STZ (55)+ Glimepiride (10)</td>
<td>208.9±19.6*</td>
</tr>
<tr>
<td>STZ (55)+ Pinacidil (1)</td>
<td>396.7±19.8*</td>
</tr>
<tr>
<td>STZ Control (55)</td>
<td>410.9±19.23*</td>
</tr>
<tr>
<td>Sertraline (30) + Pinacidil (1)</td>
<td>95.81±11.6</td>
</tr>
<tr>
<td>Sertraline (30)</td>
<td>79.5±8.15</td>
</tr>
<tr>
<td>Glimepiride (10)+ Pinacidil (1)</td>
<td>99.26±10.8</td>
</tr>
<tr>
<td>Glimepiride (10)</td>
<td>74.9±8.56</td>
</tr>
<tr>
<td>Pinacidil (1)</td>
<td>98.86±8.8</td>
</tr>
</tbody>
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*P<0.01, ANOVA followed by Dunnett’s test F (11, 60) - 105.54
hypoglycemia is possibly due to the blockade of K⁺ channels by sertraline. The hypothesis is further evidenced by the fact that K⁺ channel opener pinacidil antagonized the glimepiride and sertraline induced hypoglycemia in normal and diabetic rats. Pinacidil, per se, has no effect on blood glucose levels. On the other hand, the relaxing effects of pinacidil on KCl-induced contraction are antagonized by sertraline and glimepiride (Fig. 1).

The relaxant effect of pinacidil in intestinal smooth muscle is mediated through ATP-dependent K⁺ channels, suggesting that sertraline and glimepiride antagonized the relaxing effects of pinacidil through blockade of ATP-dependent K⁺ channels in the rat ileum. Thus, it could be possible that sertraline bind to the ATP sensitive K⁺ channels in the pancreatic β-cell membrane and inhibit channel activity depolarizing the β-cell membrane and increasing Ca²⁺ influx, hence insulin release.

It can be concluded that sertraline reduces the blood glucose levels significantly after long-term treatment. The closure of K⁺ channels is possibly involved in producing the hypoglycemia. However, further investigations on more specific tissue such as pancreas may be required to establish a direct correlation for the same.

References