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EFFECT OF SULPHONYLUREA DERIVATIVES, SPC-703 AND TOLBUTAMIDE, ON INSULIN BINDING BY ISOLATED RAT ADIPOCYTES

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The effect of oral hypoglycaemic drugs, SPC-703 [n-(p-toluenesulphonyl)-5-methyl-2-pyrazoline-1-carbonamide] and tolbutamide on insulin binding by rat adipocytes from epididymal fat pads were studied. SPC-703 and tolbutamide in concentration of 1 mM added in vitro to the suspension of adipocytes had no effect on insulin binding and kinetic parameters of insulin receptors. Daily administration of 300 mg/kg body weight of SPC-703 or tolbutamide for 10 days resulted in 48% and 34% increase of specific binding of insulin by adipocytes, respectively. From the Scatchard plot it appears that the increase of binding resulted from increased affinity of insulin receptors.
These results may explain extrapancreatic action of sulphonylurea derivatives.

Stimulation of insulin secretion by B cells of pancreatic islets is the main mechanism of hypoglycaemic action of sulphonylurea derivatives (Loubatières, 1969; Grodsky et al., 1977). However, it has been demonstrated that the increased insulin level in blood plasma resulting from the treatment with these compounds is transient and is observed only at the initial short period of the therapy (Barnes et al., 1974; Skowroński & Angielski, 1982). Chronic administration of sulphonylurea derivatives to maturity onset diabetic patients resulted in improved glucose tolerance and diabetic control, whereas the level of insulin in plasma and the ability of B cells to secrete insulin are unchanged or even decreased (Reaven & Dray, 1967; Davidson et al., 1970; Turtle, 1970; Duckworth et al., 1972; Schauder et al., 1977; Tan et al., 1977). Moreover, it was found that those sulphonylurea derivatives which were less effective stimulators of insulin secretion on prolonged administration improved glucose tolerance to the same extent as strongly active preparations (Feldman & Lebovitz, 1971). It was also demonstrated that administration to pancreatectomized animals of sulphonylurea derivatives together with small doses of exogenous insulin resulted in a greater decrease of blood glucose concentration than the administration of insulin alone (Beyer et al., 1971). This points to the existence of an additional, extrapancreatic, mechanism of the action of sulphonylurea derivatives.
There is some evidence that one of possible extrapancreatic mechanisms of action of sulphonylurea derivatives appears to be located at the level of insulin receptors in target tissues (Olefsky & Reaven, 1976; Feinglos & Lebovitz, 1978; Bachmann et al., 1979; Beck-Nielsen et al., 1979; Greenstein, 1979).

The aim of the present work was to study the effect of tolbutamide and SPC-703, a new antidiabetic drug, on the kinetics of insulin binding by isolated rat adipocytes.

MATERIALS AND METHODS

Collagenase type II series 98C 6820, crystalline bovine albumin fraction V, crystalline bovine insulin, 4-(2-hydroxyethyl)-1-piperazine-N-2-ethanesulphonic acid (Hepes) and hyamine were from Sigma Chemical Co. (St. Louis, Mo., U.S.A.). Osmium tetroxide was from Calbiochem-Behring Corp. (La Jolla, Ca., U.S.A.); 2,4,6-trimethylpyridine (collidine) was from Hopkin/Williams (England). Dimethyl phthalate was from Merek Chemical Co. (U.S.A.). Na$^{125}$I was supplied by the Institute of Nuclear Research (Świerk, Poland).

Tolbutamide was obtained from Polfa (Starogard, Poland) and, under the name of Rastinon, from Hoechst (F.R.G.). SPC-703 [n-(p-toluenesulphonyl)-5-methyl-2-pirazoline-1-carbonamide] was prepared in the Department of Chemical Technology of Drugs, Medical Academy in Gdańsk. Other reagents were supplied by POCh (Gliwice, Poland).

For radioactivity measurements, an Ultrogamma LKB Wallac gamma counter was used.

*Experimental animals.* Male Wistar rats (body weight 150 - 180 g, age 8 - 10 weeks) fed standard laboratory diet were used. The animals were divided into four groups. The animals to be used for studying the effect of sulphonylurea derivatives *in vitro* were given only the standard diet *ad libitum* (group I). The animals in the other three groups were given once daily, at 8 - 10 a.m., for 10 consecutive days, by stomach intubation, 2% starch gruel (10 ml/kg body weight), alone (group II, control) or supplemented with 300 mg/kg body weight of SPC-703 (group III) or of tolbutamide (group IV). After the last administration of the preparations, the animals were deprived of food, but had free access to drinking water. Immediately before the administration of the last dose of antidiabetic drugs, 300 μl of blood was withdrawn from the tail vein for determination of glucose; 2 h after the treatment, 500 μl of blood was collected for determination of glucose and insulin.

Glucose was determined by the orthotoluidine method according to Hultman (1959). Insulin was determined by the double antibody radioimmunological assay (Wójcikowski & Zakolski, 1974).

*Iodination of insulin.* Labelling of insulin with $^{125}$I was performed by the chloramine method of Hunter & Greenwood (1962) as modified by Dominiczak (1978). Specific activity of the iodinated preparation was 89 - 120 μCi/μg (3.3 - 4.4 MBq/μg). By this method 100% of radioactivity was precipitable by 10% trichloroacetic acid and reacted in 96% with an excess of anti-insulin antibodies.
Isolation of adipocytes. Adipocytes were isolated by the method described previously (Skowroński, 1981). The animals were killed by decapitation 2 h after administration of the last dose of starch gruel or sulphonylurea preparations. Epididymal fat pads were quickly removed and incubated in a water bath at 37°C with continuous shaking for 90 min in a polypropylene vessel containing 2.5 ml of Krebs-Ringer buffer, pH 7.4, containing 10 mm-Hepes, 0.55 mm-glucose, 3.5% (w/v) bovine serum albumin and 0.5 g/100 ml collagenase (Medium A). Usually, fat pads from one rat were used per 2.5 ml of the medium. After 90 min incubation the cells collected by filtration through two layers of nylon mesh were washed three times with warm (37°C) Krebs-Ringer solution without collagenase and glucose but containing albumin at a concentration of 1% (w/v), (Medium B). The washed cells were suspended in Medium B at the required concentration. For the experiments, aliquots of 200 μl of the cell suspension were taken with an Eppendorf pipette.

Adipocyte counts were performed using a microscope with a Fuchs-Rosenthal counting chamber as previously described (Skowroński, 1981) following the staining and fixation of the cells with osmium tetroxide by the modified method of Hirsch & Gallian (1968). The diameter (D) of the isolated adipocytes was measured using a calibrated ocular of the microscope. The cell surface (S) was calculated as $S = \pi D^2$.

Binding of insulin to isolated adipocytes. This was examined in siliconized glass vessels containing Medium B supplemented with $[^{125}]$Iinsulin at a concentration of 40 pm, 0.55 mm-glucose, unlabelled insulin at a concentration from 0.08 nm to 80 μm and other additions as indicated. The final volume of the medium was usually 500 μl and the content of cells was on the average $2 \times 10^5$ cells/ml. The incubation vessel was stoppered with a rubber stopper, immersed in a water bath and the cells were incubated with continuous shaking of 60 - 80 cycles/min for 45 min at 25°C. Then 200 μl aliquot of the cell suspension was withdrawn and transferred to plastic Beckman microtubes containing 100 μl of dinonyl phthalate, according to Gammeltoft & Gliemann (1973). The samples centrifuged for 30 s in a Beckman 152 microcentrifuge gave three layers: cells on top, oil in the middle and the medium at the bottom. The cell layer was separated by cutting the microtube with a scalpel through the oily middle layer, then the cell-bound radioactivity was determined in a gamma counter.

Specific binding was defined as the difference between the radioactivity bound to adipocytes in the absence of unlabelled insulin (total binding) and the radioactivity bound to the cells after incubation with 80 nm unlabelled insulin (unspecific binding), according to the equation:

Specific binding = total binding — unspecific binding.

All determinations were performed in duplicate.

RESULTS

Characteristics of experimental animals. No differences were observed in the weight gain between the experimental and control animals after 10 days of administration of sulphonylurea derivatives (Table 1). The glucose level in rat blood mea-
sured before administration of the last dose of the hypoglycaemic agents was in either case by about 15% lower than in the control group. The decrease in glucose concentration measured 2 h after administration of the last dose of sulphonylurea derivatives was still greater and for either of the compounds studied amounted to 50% in relation to the control group. Insulin concentration in the animals treated with SPC-703 and tolbutamide was not significantly different from that observed in control animals. No significant differences, either, were observed in the size of the adipocytes isolated from all three groups (Table 1).

Table 1

**Characteristics of experimental animals**

Glucose concentration was assayed before (T₀) and 2 h after (T₁2₀) administration of the last dose of sulphonylurea derivatives. Insulin concentration was assayed 2 h after administration of the last dose of the antidiabetic agents. The results are expressed as mean values ± S.E.M. from 6 to 24 determinations.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SPC-703</th>
<th>Tolbutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial body weight (g)</strong></td>
<td>131 ±10</td>
<td>129 ±11</td>
<td>128 ±8</td>
</tr>
<tr>
<td><strong>Final body weight (g)</strong></td>
<td>180 ±10</td>
<td>177 ±12</td>
<td>179 ±13</td>
</tr>
<tr>
<td><strong>Fat cell diameter (μm)</strong></td>
<td>44 ±10</td>
<td>42 ±11</td>
<td>43 ±10</td>
</tr>
<tr>
<td><strong>Fat cell surface (μm²×10⁻⁵)</strong></td>
<td>6.1 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>5.8 ± 0.3</td>
</tr>
<tr>
<td><strong>Blood glucose T₀ (mg/100 ml)</strong></td>
<td>75 ± 9</td>
<td>65 ±11</td>
<td>67 ±10</td>
</tr>
<tr>
<td><strong>Blood glucose T₁2₀ (mg/100 ml)</strong></td>
<td>79 ± 6</td>
<td>39 ± 7</td>
<td>40 ± 9</td>
</tr>
<tr>
<td><strong>Plasma insulin (ng/ml)</strong></td>
<td>2.1 ± 1.1</td>
<td>2.1 ± 1.1</td>
<td>2.1 ± 1.0</td>
</tr>
</tbody>
</table>

*p < 0.001; *p < 0.01; *p < 0.05 in relation to control.

_In vitro effect of SPC-703 and tolbutamide on insulin binding by adipocytes._ The two preparations of sulphonylurea derivatives at 1 mM concentration had no or little effect on insulin binding. The specific binding amounted to 1.69±0.53%, 1.47±0.12%, and 1.36±0.36% for the control group, for SPC-703-treated animals and for animals treated with tolbutamide, respectively (mean values from 4 to 6 experiments±SEM). In the presence of increasing concentrations of unlabelled insulin, specific binding of the labelled hormone was decreased, the decrease being the same in all three groups. At 40 mM concentration of unlabelled insulin this binding accounted for 0.09 - 0.12% of the total amount of [¹²⁵I]insulin (Fig. 1A). In the Scatchard (1949) plot three similar curves were obtained (Fig. 1B). The affinity constants for the cells incubated in the presence of SPC-703 were $K_a = 1.65 ± 0.1 \times 10^9 \text{ M}^{-1}$ and $K_a = 3.3 ± 0.9 \times 10^8 \text{ M}^{-1}$ ($n=6$), and in the case of tolbutamide $K_a = 1.55 ± 0.5 \times 10^9 \text{ M}^{-1}$ and $K_a = 2.3 ± 0.6 \times 10^8 \text{ M}^{-1}$ ($n=4$). These values were not much different than the kinetic parameters of binding of insulin with control cells: $K_a = 1.9 ± 0.6 \times 10^9 \text{ M}^{-1}$ and $K_a = 2.1 ± 0.6 \times 10^8 \text{ M}^{-1}$ ($n=6$). Similarly, no significant differences between the three groups of animals were observed in the number of the insulin binding sites in adipocytes.
Fig. 1. Effect of SPC-703 and tolbutamide on the binding of insulin to isolated adipocytes. The fat cells were isolated from normal rats and were incubated in the presence of 1 mM SPC-703 (○) or tolbutamide (▲). ●, Control. The results are mean values from 4-6 experiments. A, Competitive inhibition of [125I]insulin binding by increasing concentrations of unlabelled insulin. B, Scatchard plot of insulin binding. The ratio of bound to free insulin (B/F) is plotted on the ordinate and the bound insulin (B) is on the abscissa.

Fig. 2. Average affinity profile plot of insulin binding. Data are derived from Fig. 1 according to the method of De Meyts & Roth (1975). The average affinity (K) is calculated as \((B/F)/(R_o - B)\) and is plotted as a function of the log of the percent fractional occupancy \((\overline{Y})\), \((B/R_o) \times 100\).
The lack of effect of the two sulphonylurea derivatives on the affinity of the receptors for insulin in adipocytes was also confirmed by the average affinity analysis, as described by De Meyts & Roth (1975). As can be seen, the highest affinity of "empty" receptors ($K_e$) was on the average $4.0 \times 10^8 \text{ M}^{-1}$ for SPC-703 and $3.8 \times 10^8 \text{ M}^{-1}$ for tolbutamide, which is not significantly different from the control $K_e = 4.3 \times 10^8 \text{ M}^{-1}$ (Fig. 2). The lowest observed affinity ($K_f$), the affinity of filled receptors, for the three groups ranged between $0.8 \times 10^8 \text{ M}^{-1}$ and $1.2 \times 10^8 \text{ M}^{-1}$. These values were obtained at about 50% saturation of the insulin binding sites (Fig. 2).

Effect of 10-day administration of SPC-703 and tolbutamide on insulin binding by adipocytes. Administration to rats of SPC-703 or tolbutamide at a dose of 300 mg/kg body weight during 10 days caused a statistically significant increase in specific binding of insulin by isolated adipocytes. As compared to control cells, which specifically bound $1.84 \pm 0.10\%$ of the hormone, the cells obtained from SPC-703-treated or tolbutamide-treated animals bound specifically $2.72 \pm 0.16\%$ ($p < 0.001$) and $2.58 \pm 0.35\%$ ($p < 0.001$) of insulin, respectively (Fig. 3). The increase of this binding was especially pronounced at the low, physiological, insulin concentration range, i.e. 0.05 - 20 nM (Fig. 3A).

\[ \text{Insulin (nM)} \]
\[ \text{Percent insulin bound} \]
\[ \text{Bound/free insulin} \]
\[ \text{Insulin bound (pmol/2 \times 10^5 cells)} \]

Fig. 3. Effect of prolonged administration of SPC-703 and tolbutamide on the binding of insulin to isolated adipocytes. The fat cells were isolated from control animals (●) and from rats which were treated with SPC-703 (○) or tolbutamide (▲) during 10 days at a dose of 300 mg/kg body weight. The results are mean values from 6 experiments. A, Competitive inhibition of $[^{125}\text{I}]$insulin binding by increasing concentrations of unlabelled insulin. $p < 0.001$ in relation to control. B, Scatchard plot of insulin binding.

The Scatchard plots demonstrated that the increase in binding of insulin by adipocytes from the animals treated with sulphonylurea derivatives resulted from an increase in the affinity of the receptors for insulin (Fig. 3B).

In the case of SPC-703 the affinity constant $K_{a1}$ was by over 100% ($p < 0.02$) higher as compared with the control. Tolbutamide caused an about 50% ($p < 0.05$)
increase of the affinity constants (Table 2). The three groups of animals did not differ significantly in the number of the insulin receptors (Table 3).

**Table 2**

*Effect of prolonged administration of SPC-703 and tolbutamide on kinetic parameters of insulin binding to isolated adipocytes*

Mean values ±S.E.M. from 6 experiments are presented. The affinity constants ($K_a$) were determined graphically as intercept of the Scatchard plot with the ordinate, and the total receptor concentration ($R_o$) is indicated by the intercept of the plot with the abscissa.

<table>
<thead>
<tr>
<th></th>
<th>Receptors I</th>
<th></th>
<th>Receptors II</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affinity</td>
<td>Capacity</td>
<td>Affinity</td>
<td>Capacity</td>
</tr>
<tr>
<td></td>
<td>$K_a$ (M⁻¹)</td>
<td>$R_o$ (mol/2×10⁵ cells)</td>
<td>$K_a$ (M⁻¹)</td>
<td>$R_o$ (mol/2×10⁵ cells)</td>
</tr>
<tr>
<td>Control</td>
<td>1.5±0.2</td>
<td>12.2±2.9</td>
<td>1.7±0.4</td>
<td>5.0±0.9</td>
</tr>
<tr>
<td>SPC-703</td>
<td>3.1±0.6*</td>
<td>11.5±2.4</td>
<td>4.3±1.0*</td>
<td>4.0±0.7</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>2.2±0.3*</td>
<td>11.8±2.0</td>
<td>3.3±0.6*</td>
<td>4.4±0.6</td>
</tr>
</tbody>
</table>

*p < 0.02; *p < 0.05.

**Table 3**

*Effect of prolonged administration of SPC-703 and tolbutamide on the number of insulin receptors in isolated rat adipocytes*

Mean values ±S.E.M. from 6 experiments are presented. $R_o$ values are expressed as mol/2×10⁵ cells.

<table>
<thead>
<tr>
<th></th>
<th>Receptors per cell</th>
<th>Total binding sites $\times 10^{-5}$</th>
<th>Total binding sites per $1 \mu m^2$ of adipocyte surface</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>receptors I $R_{o1}$</td>
<td>$\times 10^{-4}$</td>
<td>$R_{o2}$ $\times 10^{-5}$</td>
</tr>
<tr>
<td>Control</td>
<td>3.65±0.9</td>
<td>1.50±0.3</td>
<td>1.87±0.4</td>
</tr>
<tr>
<td>SPC-703</td>
<td>3.45±0.7</td>
<td>1.21±0.2</td>
<td>1.55±0.3</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>3.54±0.6</td>
<td>1.32±0.2</td>
<td>1.67±0.3</td>
</tr>
</tbody>
</table>

The increase in the affinity of insulin receptors caused by sulphonylurea derivatives treatment was confirmed by the analysis according to De Meyts & Roth (1975). The limiting high-affinity constant ($K_a$) which is observed as occupancy approaches zero was $5.25 \times 10^8 \text{ M}^{-1}$ ($p < 0.001$) for SPC-703 and $4.75 \times 10^8 \text{ M}^{-1}$ ($p < 0.001$) for tolbutamide (Fig. 4). A significant increase in the affinity of the receptors for insulin was observed up to about 20% saturation of the total number of binding sites (Fig. 4).
Similarly as in the experiments in which the effect of sulphonylurea derivatives was studied in vitro, in the three groups studied the limiting low-affinity constants ($K_i$) did not differ and ranged from 0.5 to $1.0 \times 10^8$ M$^{-1}$ (Fig. 4).

![Graph](image)

**Fig. 4.** Average affinity profile plot of insulin binding. Data from Fig. 3. *p<0.001 in relation to control.**

**DISCUSSION**

The two sulphonylurea derivatives studied in the present work, SPC-703 and tolbutamide, did not cause any appreciable change in insulin concentration in blood when administered to rat during 10 consecutive days; however, both compounds exhibited a distinct hypoglycaemic effect. These results are in accordance with the reports of other authors for human subjects (Reaven & Dray, 1967; Davidson et al., 1970; Turtle, 1970; Druckworth et al., 1972; Barnes et al., 1974; Schauder et al., 1977; Tan et al., 1977) and point to the existence of an additional extrapancreatic mechanism of the action of sulphonylurea derivatives. Among numerous targets for the action of these preparations taken into consideration (Feldman & Lebovitz, 1969; Heptner et al., 1977) the possibility of their action on insulin receptors is now often taken into account. Such an action was demonstrated in diabetic patients treated with chlorpropamide (Olefsky & Reaven, 1976) and glibenklamide (Beck-Nielsen et al., 1979). Both these preparations caused an increase in the number of insulin receptors in monocytes of peripheral blood. It was also demonstrated that oral and subcutaneous administration of gliklikomed le to increased binding of insulin by plasma membranes of rat and mouse liver (Bachmann et al., 1979; Green-
stein, 1979); the same effect was observed after oral administration of glipizide (Feinglos & Lebovitz, 1978).

In the present work it was found that both SPC-703 and tolbutamide administered orally to rats for 10 days caused a significant increase in specific binding of insulin to adipocytes (Fig. 3A). It was also found that the increased binding was due to an increase in the affinity of the insulin receptors (Table 2). However, no distinct differences were observed in the number of receptors (Table 3). In addition, average affinity analysis according to De Meyts & Roth (1975) demonstrated that a significant increase in the affinity of receptors for insulin was observed until about 20% saturation of the total number of binding sites (Fig. 4). On the other hand, the two sulphonylurea derivatives had no effect on the kinetic parameters of insulin binding to adipocytes when SPC-703 or tolbutamide at a concentration of 1 mM was present in the incubation medium (Figs. 1, 2). Thus, the present results confirm the reports of other authors (Olefsky & Reaven, 1976; Feinglos & Lebovitz, 1978; Bachmann et al., 1979; Beck-Nielsen et al., 1979; Greenstein, 1979) who demonstrated that sulphonylurea derivatives changed the affinity of the receptors to insulin also in isolated adipocytes. They also showed that, for the appearance of this effect of sulphonylurea derivatives, a chronic administration during a few days is required. However, at variance with the reports cited above which demonstrated that the action of sulphonylureas consisted mainly in increasing the number of binding sites, the present experiments indicate that the increase in specific binding of insulin is caused by increased affinity of insulin receptors. However, it should be noted that the reports cited concern experiments with diabetic patients (Olefsky & Reaven, 1976; Beck-Nielsen et al., 1979) or with genetically obese mice (Greenstein, 1979). Both these conditions are characterized by a lowered number of insulin receptors. The present experiments were performed on normal rats having a normal number of insulin-binding sites (Table 3). The differences observed could also be due to the use of different tissue preparations as well as to the fact that sulphonylurea derivatives applied in the present research had a weaker hypoglycaemic effect. The compounds studied in the publications cited were those belonging to the second group of sulphonylurea derivatives, showing very strong hypoglycaemic properties. At present it is also difficult to interpret the fact that the effect of SPC-703 and tolbutamide became apparent only after a few days of administration. The effect of some metabolites of the sulphonylurea derivative could be taken into account (Feldman & Lebovitz, 1969; Beck-Nielsen et al., 1979) or an indirect effect through the action of other substances (Heptner et al., 1977).

The recently postulated possible effect of sulphonylurea derivatives on the microviscosity of cellular membranes (Luly et al., 1979) seems also of interest, as it has been demonstrated that an increase in the viscosity of the plasma membrane of rat liver is observed as a result of therapeutic concentration of chlorpropamide. It seems likely that lowering of the fluidity of plasma membranes in consequence of binding of antidiabetic drugs could stabilize the optimum structure of the protein complex of the insulin receptor, thus facilitating its interaction with insulin molecule (Borochov & Shinitzky, 1976; Luly & Shinitzky, 1979).
An especially interesting observation, corresponding to the effect of sulphonylurea derivatives demonstrated in the present work, is a simultaneous increase in glucose metabolism under the action of these agents (Skowroński & Angielski, 1982). Similarly as in the present experiments, the effect of SPC-703 and tolbutamide on glucose metabolism in isolated adipocytes became apparent only after a few days of therapy. On the other hand, the lack of the effect of these agents on kinetics of insulin binding to isolated adipocytes demonstrated in vitro parallels the lack of metabolic response of adipocytes. This is an important argument and confirms the known fact that the action of insulin and its biological effect depend on the binding of the hormone with the cellular receptor. Recently, Joost et al. (1982) reported a similar effect of tolbutamide on insulin binding to isolated rat adipocytes after 7 days of oral treatment. The effect was associated with an enhanced response to insulin of the adipose tissue. When added in vitro, tolbutamide failed to increase insulin binding and glucose metabolism. This, together with our data makes possible to assume that an increase in insulin binding is a general effect of sulphonylureas, but for the appearance of this effect a chronic administration of a few days duration is required.

Our results indicate also that in isolated adipocytes an increase of the affinity of insulin receptors caused by sulphonylurea derivatives could be one of the possible mechanisms of extrapancreatic action of these compounds.

REFERENCES


WPŁYW POCHODNYCH SULFONYLOMOCZNIKA, SPC-703 I TOLBUTAMIDU NA WIĄZANIE INSULINY PRZEZ IZOLOWANE KOMÓRKI TŁUSZCZOWE SZCZURA

Streszczenie

Zbadano wpływ pochodnych sulfonylomocznika, SPC-703 i tolbutamidu, na kinetykę wiązania insuliny przez komórki tłuszczowe izolowane z poduszecek tłuszczowych najadry szczura. SPC-703 i tolbutamid dodane w stężeniu 1mM do zawiesiny komórek tłuszczowych nie wpływały na parametry kinetyczne wiązania insuliny z receptorami komórkowymi. Oba sulfonylomoczniki podawane zwierzętom dożołdkowo w dawce 300 mg/kg ciężaru ciała przez 10 dni zwiększały specyficzne wiązanie insuliny przez izolowane komórki tłuszczowe średnio o 48% w przypadku SPC-703 i o 34% w przypadku tolbutamidu. Analiza Scatcharda wykazała, że wzrost wiązania jest efektem wzrostu powinowactwa receptorów insulinowych.

Wyniki te mogą wyjaśnić niezależne od trzustki działanie pochodnych sulfonylomocznika.

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