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Rapid communication

The effect of sulphonylurea on the in vivo tissue uptake of glucose in normal rats

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Summary. To evaluate the effect of sulphonylurea on in vivo tissue uptake of glucose, the arterial injection tissue-sampling technique of Oldendorf [9] was used to measure the glucose uptake of brain; liver; subcutaneous fat; and of three skeletal muscles, the masseter, femoris and soleus. Rats gavaged with glipizide 5 mg/kg daily for 5 days were compared to vehicle-treated rats. The serum glucose levels at the time of the experiment were identical in the two groups (10.36 ± 0.42 mmol/l vs 10.38 ± 0.36 mmol/l). Glipizide treatment did not result in an increase in glucose uptake by the various tissues studied. It is concluded that, under physiological conditions in non-fasted rats, sulphonylureas do not significantly alter tissue uptake of glucose.

Key words: Sulphonylureas, glucose, glipizide.

The precise mechanism of action of sulphonylureas is still not clear. Whereas short-term administration results in increased insulin secretion [1, 2], the long-term antidiabetic action is attributed mostly to extra pancreatic effects [3, 4]. Sulphonylureas increase the number of insulin receptors [5] and potentiate insulin-mediated recruitment of glucose carriers in isolated adipocytes [6]. In vivo evidence for sulphonylurea potentiation of insulin mediated glucose clearance has relied on the plasma glucose response to exogenously administered insulin [5, 7], and the effect of improved diabetes control per se on glucose disposal rate [7, 8] has been underestimated.

To determine the effect of sulphonylureas on the tissue uptake of glucose in vivo under physiological conditions in non-fasted rats, single arterial injection tissue-sampling technique was used to determine the glucose uptake in various tissues.

Methods

Male Fisher 344 rats (200–230 g) were used. One group of rats was given glipizide (Pfizer Pharmaceuticals, Inc, Groton, Connecticut, USA; 5 mg/kg daily by gavage for 5 days), and the control group was gavaged with the same volume (0.5 ml) of the vehicle (60% polyethylene glycol in phosphate buffer). None of the rats developed diarrhea or any untoward side effects. All the experiments were carried out within 3 h of the last dose of glipizide. The tissue uptake of glucose was determined by Oldendorf's method [9], using ^{14}C-D-glucose (specific activity 356 mCi/mmol) as the test ligand and $^{3}H_2O$ (luci/μl) as the internal diffusible reference substance. The radiolabelled isotopes were purchased from New England Nuclear, Boston, Mass., USA. The radio chemical purity of ^{14}C-D-glucose was 98% by paper chromatography. The tissue uptake index (TUI) of glucose was determined as:

$$TUI = \frac{(^{14}C \text{ dpm}/^{3}H \text{ dpm}) \text{ tissue} \times 100}{(^{14}C \text{ dpm}/^{3}H \text{ dpm}) \text{ injectate}}$$

0.2 ml (the exact volume is immaterial) of 10 mmol/l HEPES buffered Ringer's saline (pH = 7.4) containing 0.4 μCi of ^{14}C-D-glucose and 2 μCi of $^{3}H_2O$ was injected either in the right common carotid artery, or hepatic portal vein after the ligation of the hepatic artery, or in the aorta immediately above the bifurcation; 15 s later either the animal was decapitated, or a piece of the right lobe of the liver was excised, or the right lower extremity was amputated. The tissues of interest were solubilized in 1.5 ml Soluene (Packard Instrument Co, Downers Grove, Illinois, USA) at 60 °C for 2 to 3 h. Ten ml of scintillation cocktail (Instagel, Packard Instrument Co, Downers Grove, Illinois, USA) was added and the radioactivity of ^{3}H and ^{14}C counted simultaneously. The counts per minute (cpm) were converted to true disintegrations per minute (dpm) after appropriate corrections were made for ^{14}C count spillover in ^{3}H window. The results are expressed as mean ± SEM. Statistical analysis was done with the Student's t-test using Dunnett's Convention. A p value of < 0.05 was considered statistically significant.

Results

The mean serum glucose level at the time of the experiment in glipizide treated rats (10.36 ± 0.42 mmol/l) was not significantly different from the control rats (10.38 ± 0.36 mmol/l). The glucose uptake index of various tissues was not significantly different in the glipi-

Table 1. Tissue glucose uptake index (%)

Tissue	(*n*)	Control	(*n*)	Glipizide treated
Brain	6	33.3±3.1	6	36.7±2.2
Liver	3	23.5±1.6	3	23.5±2.9
Subcutaneous fat (from the thigh)	5	14.5±3.8	5	11.7±2.2
Masseter muscle	6	21.3±6.1	6	18.8±2.4
Femoris	4	30.2±6.1	4	32.4±0.8
Soleus	4	34.1±6.1	4	29.1±4.5

Results are given as mean±SEM

zide treated rats compared to vehicle administered controls. Table 1 summarizes the results of glucose TUI.

Discussion

Although studies in isolated adipocytes in vitro have suggested that sulphonylureas enhance insulin-stimulated glucose transport [6], the biological significance of these observation at the organism level is not clear. On the other hand, the clinical studies could not distinguish the effect of improved diabetic condition from a possible direct effect of sulphonylureas on the glucose disposal rate [7, 8]. The present study evaluates tissue glucose uptake under physiological conditions and in the absence of acute variations of serum glucose or insulin. Chronic glipizide treatment did not enhance glucose uptake in either insulin sensitive or insensitive (brain) tissues. It is possible, though unlikely, that the glucose uptake by adipose tissue at a different site could have been increased. Despite the fact that differences among various skeletal muscles in insulin binding capacity and glucose uptake [10] are well recognized, the glucose uptake by three different muscle types was not altered by glipizide therapy. Thus, it appears that in vivo biological impact of glipizide on glucose transport system is minor, and may only be detected when amplified by exogenous insulin administration.

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References

1. Pfeiffer EF, Pfeiffer M, Ditschuneit H, Ahn CS (1959) Clinical and experimental studies of insulin secretion following tolbutamide and metehexamide administration. Ann NY Acad Sci 82: 479-495
2. Yalow RS, Black H, Villazon M, Berson SA (1960) Comparison of plasma insulin Levels following administration of tolbutamide and glucose. Diabetes 9: 356-362
3. Levey GS (1977) The effects of sulfonylureas on peripheral metabolic process. Fed Proc 36: 2720-2723
4. Duckworth WC, Solomon SS, Kitabchi AE (1972) Effect of chronic sulfonylurea therapy on plasma insulin and proinsulin levels. J Clin Endocrinol Metab 35: 585-591
5. Feinglos MN, Lebovitz HE (1978) Sulphonylureas increase the number of insulin receptors. Nature 276: 184-185
6. Jacobs DB, Jung CY (1985) Sulfonylurea potentiates insulin-induced recruitment of glucose transport carrier in rat adipocytes. J Biol Chem 260: 2593-2596
7. Greenfield MS, Doberne L, Rosenthal M, Shulz B, Widstrom A, Reaven GN (1982) Effect of sulfonylurea treatment on *in vivo* insulin secretion and action in patients with non-insulin dependent diabetes mellitus. Diabetes 31: 307-312
8. Verdonk CA, Rizza R, Gerich JE (1981) Effects of plasma glucose on glucose utilization and glucose clearance in normal man. Diabetes 30: 535-537
9. Oldendorf WH (1970) Measurement of brain uptake of radiolabelled substances using a tretiated water internal standard. Brain Res 24: 372-376
10. Bonen A, Tan MH, Watson-Wright WM (1981) Insulin binding and glucose uptake differences in rodent skeletal muscles. Diabetes 30: 702-704

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