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Interference of sulphonylurea antidiabetica with mitochondrial bioenergetics under *in vivo* conditions[1]

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Sulphonylurea antidiabetica effectively inhibits the basal hepatic glucose production. Since it has been firmly established that lipophylic sulphonylurea drugs exerted an uncoupling effect on mitochondrial oxidative phosphorylation, a relationship between the reduction of hepatic gluconeogenesis and the insufficient energy supply due to sulphonylureas could be supposed. In this study we have investigated the effects of glibenclamide and gliquidone on mitochondrial bioenergetics in liver after peroral treatments of normal rats with different doses. The treatment of rats with 5 mg/kg glibenclamide or gliquidone daily for 14 days elicited only a marginal inhibition on mitochondrial oxidation capacity and remained without any effect on mitochondrial ATPase activity. Only the supermaximal dose 50 mg/kg for 14 day produced a significant damage in the mitochondrial functions. The basal respiration increased with 60–80 per cent, whereas the ADP- or DNP-stimulated oxygen consumption significantly decreased independently from the respiratory substrates investigated. Similar alterations were found in the mitochondrial ATPase activity after treatment with these drugs. No essential differences have been observed in the actions between glibenclamide and gliquidone.

However, the lowest dose applied in this study is many times higher than the usual therapeutic dose. Consequently, glibenclamide and gliquidone do not interact with mitochondrial bioenergetic processes under therapeutic conditions. On the other hand, in different liver and kidney damages we have no sufficient knowledge whether these drugs can be accumulated in these organs and therefore their elevated concentration may interfere with the mitochondrial energy metabolism.

Keywords: sulphonylurea antidiabetica, glibenclamide, gliquidon, mitochondrial bioenergetics, *in vivo* effects

[1] This paper is dedicated to the memory of Professor Tibor Kovács (1929–1994)

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Sulphonylurea antidiabetic drugs are widely used in treatment of non-insulin dependent diabetes mellitus to stimulate insulin release from pancreatic cells [1, 2]. This effect is associated with an increased number of insulin receptors [3, 18, 42, 49] and an enhanced insulin mediated glucose utilization [2, 5, 14, 26, 31, 37]. Furthermore, sulphonylureas reduce the basal hepatic glucose production [5, 26].

Not only the anti-hyperglycaemic action of sulphonylurea but their pharmacokinetics and metabolism have been also intensively studied [6, 7, 10, 11, 21, 22, 28, 43, 44]. The widely used sulphonylureas gliquidone and glibenclamide are rapidly absorbed, their elimination from plasma occurs also quickly [13, 28, 46]. The biological half-life proved to be similar in both cases [10, 20, 28]. Both drugs are extensively metabolized in the liver. Three main metabolites of glibenclamide and four derivates of gliquidone were isolated. The metabolites had no hypoglycaemic effect. Elimination of glibenclamide is equally mediated by the urine and faeces. However, excretion of gliquidone occurs in 90 per cent via bile, in the urine no more than 5 per cent of its inactive metabolite can be detected [13, 28, 36].

In our previous paper the possible interference of gliquidone and glibenclamide with mitochondrial bioenergetics was studied [45]. We have established that under *in vitro* conditions these sulphonylureas exerted a partial uncoupling effect on mitochondrial respiration of liver and they inhibited the DNP-activated ATPase and the substrate uptake into mitochondria. These effects proved to be dose dependent [45]. Although many changes in mitochondrial functions under *in vitro* conditions have been published [15, 32, 34, 45, 47], a detailed analysis of *in vivo* alteration of mitochondria following sulphonylurea treatment has not been performed so far. In this study the effects of glibenclamide and gliquidone on the mitochondrial bioenergetics of rats are investigated after peroral treatment with different doses of sulphonylurea tested.

Materials and Methods

Male CFY rats weighing 150–180 g (LATI, Gödöllő, Hungary) were used for experiments. The animals were appropriately housed and fed a corresponding laboratory diet supplemented with vitamin premix and water *ad lib*.

The rats were treated with a single dose of 50 mg/kg of the respective sulphonylurea intraperitoneally, suspended freshly in 1 per cent methylcellulose (Aldrich Chemical Co.). Two hours after the drug administration the rats were killed and liver mitochondria were isolated. Other groups of rats were treated with 5 mg or 50 mg/kg drugs *per os* for two weeks once daily. To control animals only methylcellulose was administered. All other methods used in this study were described previously [45].

Results

The influence of gliquidone and glibenclamide on mitochondrial respiration capacity

To test whether gliquidone as well as glibenclamide influence the mitochondrial ATP generation and therefore the energy dependent metabolic pathways of the cells under *in vivo* conditions, their effects were investigated on respiration capacity of rat liver mitochondria after treatments with different doses of the drugs.

An administration of 5 mg/kg glibenclamide or gliquidone to the rats for 14 days, did not alter the basal as well as the ADP- or DNP-stimulated respiration in comparison with the control values using different respiratory substrates (Tables I–III).

When a supermaximal dose (50 mg/kg) of gliquidone or glibenclamide was administered to the rats intraperitoneally, the respiratory parameters of the isolated liver mitochondria were only slightly affected two hours after the treatment. Glibenclamide caused a little but measurable increase in the basal respiration, gliquidone treatment was without effect in the case of all respiratory substrates tested. In the ADP- as well as DNP-stimulated O_2-uptake no changes was observed at these doses of both drugs (Tables I–III).

Table I

Mitochondrial respiration of liver mitochondria with glutamate + malate

No. of experiments	Pretreatment	Oxygen uptake (nAtom O/mg protein/min) Basal	ADP-stimulated	DNP-stimulated	RCR
10	Control	14 ± 2	195 ± 20	188 ± 19	13.9
6	5 mg/kg glibenclamide p.o. 14 days	15 ± 2	196 ± 21	186 ± 18	13.1
10	50 mg/kg glibenclamide i.p. 2 hours	17 ± 3	198 ± 19	191 ± 19	11.6
6	50 mg/kg glibenclamide p.o. 14 days	23* ± 3	157* ± 17	146* ± 15	6.8
6	5 mg/kg gliquidone p.o. 14 days	14 ± 2	196 ± 18	187 ± 18	14.0
12	50 mg/kg gliquidone i.p. 2 hours	15 ± 2	199 ± 18	191 ± 19	13.3
6	50 mg/kg gliquidone p.o. 14 days	23* ± 3	170* ± 17	164* ± 17	7.4

* Significance: $p < 0.05$

Table II

Mitochondrial respiration of liver mitochondria with pyruvate + malate

No. of experiments	Pretreatment	Oxygen uptake (nAtom O/mg protein/min) Basal	ADP-stimulated	DNP-stimulated	RCR
10	Control	10 ± 2	102 ± 9	98 ± 10	10.2
6	5 mg/kg glibenclamide p.o. 14 days	11 ± 2	102 ± 2	98 ± 10	9.3
10	50 mg/kg glibenclamide i.p. 2 hours	12 ± 2	98 ± 10	86 ± 9	8.9
6	50 mg/kg glibenclamide p.o. 14 days	17* ± 3	75* ± 9	69* ± 8	4.4
6	5 mg/kg gliquidone p.o. 14 days	11 ± 2	102 ± 9	98 ± 9	9.3
12	50 mg/kg gliquidone i.p. 2 hours	11 ± 2	104 ± 10	83 ± 9	9.5
6	50 mg/kg gliquidone p.o. 14 days	18* ± 3	76* ± 8	71* ± 8	4.2

* Significance: $p < 0.05$

Table III

Mitochondrial respiration of liver mitochondria with succinate (in the presence of rotenone)

No. of experiments	Pretreatment	Oxygen uptake (nAtom O/mg protein/min) Basal	ADP-stimulated	DNP-stimulated	RCR
10	Control	40 ± 5	290 ± 31	264 ± 28	7.3
6	5 mg/kg glibenclamide p.o. 14 days	41 ± 6	293 ± 32	264 ± 27	7.1
10	50 mg/kg glibenclamide i.p. 2 hours	44 ± 5	301 ± 32	264 ± 27	6.8
6	50 mg/kg glibenclamide p.o. 14 days	47* ± 6	239* ± 26	201* ± 23	5.1
6	5 mg/kg gliquidone p.o. 14 days	41 ± 5	291 ± 30	265 ± 28	7.1
12	50 mg/kg gliquidone i.p. 2 hours	41 ± 4	297 ± 30	239 ± 25	7.2
6	50 mg/kg gliquidone p.o. 14 days	46* ± 5	283* ± 31	231* ± 25	6.2

* Significance: $p < 0.05$

Table IV

ATPase activity of isolated liver mitochondria

No. of experiments	Pretreatment	ATPase activity (μmoles P_i/mg protein/h) Basal	DNP-stimulated
8	Control	1.74 ± 0.21	18.93 ± 2.11
6	5 mg/kg glibenclamide p.o. 14 days	1.72 ± 0.19	18.84 ± 2.06
6	50 mg/kg glibenclamide i.p. 2 hours	1.89 ± 0.34	18.61 ± 2.43
6	50 mg/kg glibenclamide p.o. 14 days	2.27 ± 0.41*	12.39 ± 2.08*
6	5 mg/kg gliquidone p.o. 14 days	1.69 ± 0.20	18.96 ± 2.10
6	50 mg/kg gliquidone i.p. 2 hours	1.65 ± 0.33	18.90 ± 2.11
6	50 mg/kg gliquidone p.o. 14 days	1.97 ± 0.34	12.35 ± 1.83*

* Significance: $p < 0.05$

After a treatment of 14 days with the same doses of both glibenclamide and gliquidone substantial alterations were seen in the mitochondrial respiration. The basal respiration increased by 60–80 per cent when glutamate or pyruvate with malate were used as substrates. Interestingly, the one-step oxidation of succinate was elevated less than 20 per cent under the same conditions (Tables I–III). The ADP- as well as DNP-stimulated respiration was reduced by 25 per cent maximally. As a result of the opposite changes of the respiration values with and without added ADP, the respiratory control ratios decreased significantly. With glutamate or pyruvate in the presence of malate, the decrease of RCR value exceeded 50 per cent, while the change in the RCR value with succinate was less pronounced (Tables I–III).

Effect of gliquidone and glibenclamide on the mitochondrial ATPase activity

Gliquidone and glibenclamide induced similar changes of the ATPase activity of liver mitochondria to those of the respiration. After two hours of the intraperitoneal administration of 50 mg/kg glibenclamide or gliquidone, no substantial alteration of mitochondrial ATPase activity was observed. Similarly, no changes in ATPase activity of mitochondria were observed when 5 mg/kg of the drugs were administered to the rats for 14 days (Table IV). A treatment of 14 days with supramaximal dose (50 mg/kg) of the drugs caused a 15–30 per cent increase in the basal ATPase activity and a near 40 per cent reduction in the DNP-stimulated ATPase activity (Table IV). No significant difference was observed between gliquidone and glibenclamide in their

inhibitory potential upon mitochondrial ATPase. The alterations in mitochondrial ATPase activities observed supported further a potential damage of structural integrity of mitochondria due to sulphonylureas under *in vivo* conditions.

Discussion

In the last more than 30 years sulphonylurea compounds have been widely used in the treatment of patients with non-insulin-dependent diabetes mellitus. These drugs act at both pancreatic and extrapancreatic sites. However, it seems likely that the initial and quantitatively most important action of the sulphonylureas is the stimulation of insulin secretion [3, 9, 12, 19, 27, 30]. Among the extrapancreatic effects the reduction of hepatic glucose production and the increase of the insulin dependent glucose uptake into the insulin sensitive tissues are the most important [2–4, 8, 11, 16, 40, 48]. Using cultured rat hepatocytes the stimulation of glycogenesis and lipogenesis under influence of sulphonylurea drugs was also observed [14, 17, 37, 38, 39, 41]. In the hepatic glucose production the gluconeogenesis plays the cardinal role. This process involves both the mitochondrial and cytosolic compartments of the cells and can be influenced at many different sites. The transport of metabolites between cytosol and mitochondria, the availability of precursor molecules and reducing equivalents, and the supply with ATP are probably the most important factors which can alter the intensity of the gluconeogenesis. On the other hand, the actual concentration of fructose 2,6-bisphosphate determines the direction of metabolic processes to synthesis or to degradation of glucose. For the synthesis and breakdown of fructose 2,6-bisphosphate the same bifunctional enzyme is responsible, the phosphorylated state of this enzyme determines in which direction the enzyme acts. It was demonstrated from many sites that sulphonylureas can stimulate fructose 2,6-phosphate formation in liver even in streptozotocin induced diabetic rats [4, 23–25, 33, 35].

The energy supply of gluconeogenesis meet demands by the intensive oxidation of fatty acids as well as citrate cycle intermediates in mitochondria. Different uncouplers of oxidative phosphorylation increase the utilization of mitochondrial metabolites without utilisable energy production. In the previous paper we have demonstrated that sulphonylurea compounds can cause a partial uncoupling of oxidative phosphorylation [45]. This finding was supported by earlier observations, too [15, 32, 47]. Sulphonylureas can penetrate through plasma membrane and are detectable also in mitochondria [46]. It can be supposed that the mitochondrial inner membrane can bind the lipophyl sulphonylurea compounds and the non-specific interference with the lipid bilayer can cause disturbances in the function of the integral membrane proteins.

Although the therapeutic dose is less for glibenclamide than for gliquidone, we have not found a significant difference in their inhibitory capacity upon mitochondrial bioenergetic processes either *in vitro* or *in vivo*. The daily treatment with 5 mg glibenclamide or gliquidone/kg of the normal rats for 14 days elicited only a marginal

inhibition in the mitochondrial oxidation capacity. Only the supermaximal dose from these drugs (50 mg/kg) produced a significant inhibition of oxidative parameters. The concentrations of sulphonylureas investigated in this study are not comparable with the usual therapeutic doses, therefore the relevance of the mitochondrial effects to human clinical pharmacology remains to be clarified. Certainly, our results suggest that both gliquidone and glibenclamide do not interact with the mitochondrial bioenergetic processes in therapeutic dosages under *in vivo* conditions. However, in different liver or kidney damages we have no sufficient information whether these drugs can be accumulated, and therefore their local concentration may interfere with mitochondrial bioenergetics in these organs.

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