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Suramin-induced reciprocal changes in glucose and lactate synthesis in renal tubules contribute to its hyperglycaemic action

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Abstract

Suramin is the drug of choice for the treatment of African trypanosomiasis and onchocerciasis. It is also tested for its potential use as an anticancer agent and chemosensitizer. As suramin has been reported to induce hyperglycaemia, its effect on glucose formation has been studied in isolated rabbit hepatocytes and kidney-cortex tubules. In contrast to hepatocytes, in kidney-cortex tubules suramin augments glucose production and decreases lactate formation. Suramin-induced changes in intracellular gluconeogenic/glycolytic intermediates indicate a decrease in flux through pyruvate–phosphoenolpyruvate step. Moreover, this compound diminishes pyruvate kinase activity in kidney-cortex cytosolic fraction, while fructose-1,6-bisphosphate ameliorates its inhibitory action. As (i) kidneys are important contributors to the whole body glucose homeostasis and (ii) suramin is known to accumulate in kidney, suramin-induced stimulation of glucose formation in renal tubules might be responsible for hyperglycaemia observed in patients undergoing suramin treatment.

Keywords: Suramin; Hyperglycaemia; Glucose formation; Renal tubules; Pyruvate kinase; (Rabbit)

1. Introduction

Suramin, a polysulphonated naphtylurea, has been noted to exhibit trypanocidal activity becoming the drug of choice for treatment of African trypanosomiasis and onchocerciasis since 1924 (Hawking, 1978). Several other effects of this drug have also been reported, such as: inhibition of reverse transcriptase (Mitsuya et al., 1984), P2X and P2Y nucleotide receptor families antagonism (Dunn and Blakeley, 1988), blocking action of various growth factors (fibroblast growth factors, platelet derived growth factors, transforming growth factors alpha and beta and insulin growth factor I) (Olivier et al., 1990; Hosang, 1985; Kim et al., 1991; Pollak and Richard, 1990). As suramin hinders proliferation and migration of cells as well as the formation of new blood vessels it is tested for its potential use as an anticancer agent and chemosensitizer (Gasparini, 1999; Ogden et al., 2004; Xin et al., 2005). As suramin has also been noted to induce hyperglycaemia (Kaur et al., 2002 for review), the aim of this investigation was to study its effect on glucose formation in hepatocytes and kidney-cortex tubules isolated from rabbit, which exhibit a similar localisation of gluconeogenic enzymes to that of the human (Usatenko, 1970).

2. Materials and methods

2.1. Chemicals

Enzymes and nicotinamide adenine dinucleotides were obtained from Roche (Mannheim, Germany). High Performance Liquid Chromatography (HPLC) solvents were purchased from Merck (Darmstadt, Germany) and were of gradient or HPLC grade. Other chemicals were from Sigma and were of the highest purity available. Silicon oils AR20 and AR 200 for tubule separation from the reaction medium were generous gifts of Brenntag-Polska.

2.2. Preparation and incubation of kidney-cortex tubules

Male white Termond rabbits were used throughout. Animals were maintained on standard rabbit chow with free access to water and food. All procedures adhered to European

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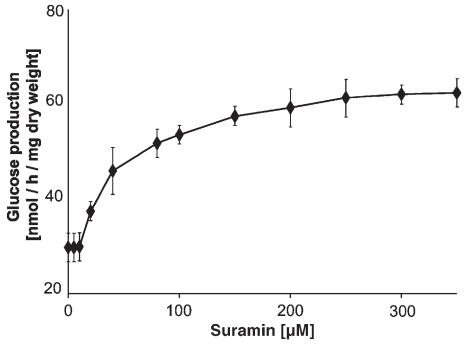

Fig. 1. The effect of suramin concentration on glucose formation in the kidney-cortex tubules incubated with 2 mM aspartate and 2 mM glycerol. Values are means±S.D. represented by vertical lines for four separate experiments.

Community guidelines for the use of experimental animals and were approved by the First Warsaw Local Commission for the Ethics of Experimentation on Animals. The experiments were performed with the use of renal tubules and hepatocytes isolated from 48 h fasted male rabbits (2–3 kg body weight) to enhance glucose production and deplete intracellular glycogen stores, thus excluding the possibility that observed effects are due to alternations in glycogen metabolism (Zaleski and Bryla, 1978; Zablocki et al., 1983). At the end of the procedures, the tubules were suspended in about 15 ml of the Krebs-Ringer bicarbonate buffer and immediately used for incubation.

Since rabbit kidney-cortex tubules do not produce glucose from aspartate or alanine as sole substrates, 2 mM aspartate was added in the presence of 2 mM glycerol with or without 0.5 mM octanoate while 2 mM alanine was included in the presence of both 2 mM glycerol and 0.5 mM octanoate (Lietz and Bryla, 1995; Lietz et al., 1999). The tubules and hepatocytes were incubated at 37 °C in 2 ml of the Krebs-Ringer bicarbonate buffer (pH 7.4) in 25 ml plastic Erlenmeyer flasks under the atmosphere of 95% O_2+ 5% CO_2 in the presence of substrate concentrations indicated in legends to figures and tables. For measurement of the total production of metabolites in renal tubule suspension, the reaction was terminated after 60 min of incubation by the addition of 35% perchloric acid (0.1 vol. of suspension). Both intracellular and extracellular levels of metabolites were measured in 1 ml samples withdrawn from the reaction medium after 60 min of incubation and centrifuged through the silicon oil into 12% perchloric acid solution as described previously (Lietz and Bryla, 1995).

2.3. Analytical methods

Total glucose was measured by the method described by Bergmeyer and Bernt with the use of glucose oxidase, peroxidase and o-dianisidin (Bergmeyer, 1983). Intracellular gluconeogenic metabolites and lactate were quantified enzymatically (Bergmeyer, 1983) either fluorimetrically or spectrophotometrically, by following changes in NAD(P)H absorbance at 340 nm or fluorescence at 465 nm (excitation 340 nm). Amino acids were determined by HPLC after derivatization of samples with 4-dimethylaminoazobenzene-4′-sulphonyl chloride (DABS-Cl) as described by Chang et al. (1983). Cytosol for the determination of pyruvate kinase activity was obtained according to Pilkis et al. (1978). Pyruvate kinase activity was assessed according to the method described by Bücher and Pfleiderer (1955) and modified by Tietz and Ochoa (1958).

2.4. Statistical analysis

Experimental values are presented as means±S.D. The number of experiments per group is indicated in the legends to tables and figures. Statistical analysis was carried out by the Students *t* test, the $P<0.05$ was considered as statistically significant.

3. Results

3.1. The effect of suramin on glucose formation, lactate production and amino acid metabolism in isolated kidney-cortex tubules and hepatocytes

To test the effect of suramin on glucose formation, kidney-cortex tubules and hepatocytes were incubated with suramin in the presence of various gluconeogenic substrates. In the presence of aspartate+glycerol a significant stimulatory action of suramin on glucose formation in kidney-cortex tubules was observed at 50 μM suramin, whereas increased concentrations of this compound up to 200 μM caused an acceleration of glucose production by about 170% compared to control values (Fig. 1). An elevation of suramin concentration above 200 μM did not significantly change the suramin action. Thus, in further experiments this compound was added at 200 μM concentration.

The action of suramin on gluconeogenesis in renal tubules was dependent upon the substrates used as glucose precursors

Table 1
The effect of 200 μM suramin on glucose and lactate synthesis in kidney-cortex tubules incubated with various substrates

Substrates	Glucose formation [nmol/h/mg dw.]		Lactate synthesis [nmol/h/mg dw.]	
	− Suramin	+Suramin	− Suramin	+Suramin
Aspartate+glycerol	33.1±5.2	57.3±6.4[a]	306.3±11.6	210.7±10.2[a]
Aspartate+glycerol+octanoate	133.7±10.6	134.7±12.7	45.8±8.0	48.5±7.3
Dihydroxyacetone	35.9±4.7	48.3±6.3[a]	509.4±13.8	425.7±12.6[a]
Dihydroxyacetone+octanoate	152.9±9.6	165.3±8.0	nd.	nd.
Alanine+glycerol+octanoate	57.9±5.3	56.3±3.8	261.4±9.9	280.8±10.8
Pyruvate	84.2±9.1	86.4±9.5	74±5.4	78±5.6

The values are means±S.D. for at least 4 separate experiments. Alanine, aspartate and glycerol were added at 2 mM concentrations, while dihydroxyacetone, pyruvate and octanoate were included at 5, 5 and 0.5 mM concentrations, respectively. Suramin was present at 200 μM concentration where indicated. [a]$P<0,05$ versus no suramin in the incubation medium. nd.—not determined.

(Table 1). With either aspartate+glycerol or dihydroxyacetone suramin caused stimulation of glucose production amounting to about 170% and 130% of the control value, respectively, while with pyruvate and malate it had no effect on glucose formation. Suramin did not affect glucose production when octanoate, a strong activator of gluconeogenesis, was added to the incubation mixture in the presence of aspartate+glycerol or alanine.

In kidney-cortex tubules 200 μM suramin diminished lactate production in the presence of aspartate+glycerol and dihydroxyacetone by about 30% and 15%, respectively. Similarly, with glucose as glycolytic substrate 200 μM suramin decreased lactate formation from 287.4±21 to 186.5±17 nmol/h/mg dry weight. No influence of suramin on lactate output was observed in the presence of alanine+glycerol+octanoate or aspartate+ glycerol+octanoate as gluconeogenic substrates, i.e. under conditions in which suramin did not stimulate glucose production. Thus, in kidney-cortex tubules suramin-induced decline of lactate production is only observed under conditions of increased glucose output. Moreover, suramin resulted in a decreased alanine formation by about 30%, (from 72±11 nmol/h/mg dry weight to 59±9 nmol/h/mg dry weight, $P<0.05$) whereas it altered neither glutamate (57±6 nmol/h/mg dry weight in control versus 59±5 nmol/h/mg dry weight in the presence of suramin) nor glutamine synthesis (68±6 nmol/h/mg dry weight in control versus 67±5 nmol/h/mg dry weight in the presence of suramin).

Surprisingly, in contrast to kidney-cortex tubules, inclusion of suramin into the incubation medium containing hepatocytes did not affect glucose formation independently on utilized substrates (Table 2).

3.2. Suramin-induced changes in gluconeogenic and glycolytic intermediates

In order to identify steps of both gluconeogenesis and glycolysis responsible for the changes induced by suramin in renal glucose metabolism the intracellular levels of gluconeogenic and glycolytic intermediates have been measured in the presence of dihydroxyacetone, as this substrate is readily utilized for both glucose and lactate synthesis. As shown in Fig. 2, on the addition of suramin an elevation of phosphoenolpyruvate and glucose levels by 100% and 40%, respectively, was accompanied by a fall of the pyruvate level down to 78% of the control value, while the levels of other intracellular metabolites were close to control values. Such changes indicate a decrease in the rate of glycolysis accompanied by a stimulation of gluconeogenesis at the level of pyruvate–oxalacetate–phosphoenolpyruvate futile cycle, probably due to either a decrease in the pyruvate kinase activity or increase in phosphoenolpyruvate carboxykinase activity.

Table 2
The effect of 200 μM suramin on glucose synthesis in hepatocytes incubated with various substrates

Substrates	Glucose formation [nmol/h/mg dw.]	
	− Suramin	+Suramin
Alanine	25.8±3.6	27.6±4.2
Alanine+glycerol+octanoate	53.1±4.3	55.3±3.1
Pyruvate	54.1±6.2	56.9±6.3
Lactate	73.0±5.9	75.2±8.0
Dihydroxyacetone	115.5±9.5	115.7±11.2

The values are means±S.D. for at least 4 separate experiments. Alanine, dihydroxyacetone, lactate and pyruvate were added at 5 mM concentrations, while glycerol and octanoate were included at 5 and 0.5 mM concentrations, respectively. Suramin was present at 200 μM concentration where indicated.

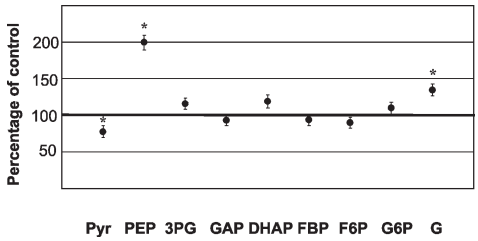

Fig. 2. Suramin-induced changes in intracellular gluconeogenic and glycolytic intermediates in rabbit kidney-cortex tubules incubated with 2 mM dihydroxyacetone. Data are expressed as percentage of control values±S.D. represented by vertical lines for four separate experiments. *$P<0.05$ versus the control values with no suramin. Metabolites listed from left to right exhibit the following control values in nmol/h/mg dry weight±S.D.: pyruvate (Pyr): 1.06±0.11; phosphoenolpyruvate (PEP): 0.16±0.04; 3-phosphoglycerate (3PG): 1.81±0.12; glyceraldehyde-3-phosphate (GAP): 0.16±0.03; dihydroxyacetone phosphate (DHAP): 0.91±0.09; fructose-1,6-bisphosphate (FBP): 0.97±0.12; fructose-6-phosphate (F6P): 1.18±0.10; glucose-6-phosphate (G6P): 0.65±0.08; glucose (G): 12.77±1.05.

3.3. The effect of suramin on pyruvate kinase activity

Since phosphoenolpyruvate carboxykinase activity in cytosolic fraction was not increased by suramin (data not shown), the action of this chemical on pyruvate kinase activity has been investigated in the cytosolic fraction of the kidney cortex.

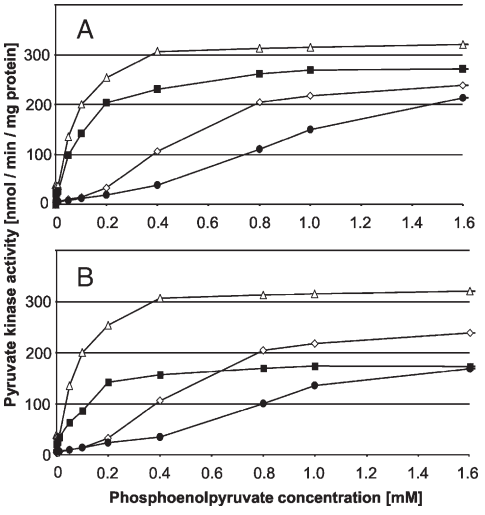

Fig. 3. Pyruvate kinase activity in the cytosolic fraction of rabbit kidney cortex in the absence and presence of 5 μM (A) and 25 μM (B) suramin without or with 0.1 mM fructose-1,6-bisphosphate. ◇ Control, △ +fructose-1,6-bisphosphate, ● + suramin, ■ + suramin+fructose-1,6-bisphosphate. Data represent a typical experiment which was reproduced at least 3 times with similar results.

Suramin caused inhibition of the enzyme activity by about 10% and 30% at 5 and 25 μM concentrations, respectively (Fig. 3). Higher levels of suramin were not tested due to the considerable light absorbance of the compound at 340 nm. At 0.1 mM concentration fructose-1,6-bisphosphate, an allosteric activator of pyruvate kinase (Irving and Williams, 1973) ameliorated the inhibitory action of 5 μM suramin. Moreover, at 25 μM concentration of this chemical, fructose-1,6-bisphosphate abolished the inhibitory action of suramin at phosphoenolpyruvate concentrations below 0.8 mM. In view of these data it is likely that suramin might be considered as an allosteric inhibitor of the renal pyruvate kinase.

4. Discussion

Suramin is currently used in therapy of several parasitic diseases, mainly African trypanosomiases. It is also considered as a potential drug in the treatment of several tumors and viral diseases (Burchmore et al., 2002; Gasparini, 1999; Kaur et al., 2002; Ogden et al., 2004). There are known side effects of suramin as a drug: lethargy, rash, anemia, hypocalcaemia, hyperglycaemia, coagulopathy, neutropenia and renal and hepatic complications (Kaur et al., 2002 for review). In agreement with the commonly accepted view that even transient hyperglycaemia poses a threat to health and can trigger/accelerate the development of diabetes due to a variety of actions cumulatively named as glucotoxicity (Rebolledo and Actis Dato, 2005), the present investigation focuses on the effect of suramin on gluconeogenesis as a possible cause of hyperglycaemic action of this compound (Kaur et al., 2002). As kidneys are important contributors of systemic glucose (Gerich et al., 2001), suramin-induced activation of glucose production in kidney-cortex tubules (Table 1 and Fig. 1) could disturb the whole body glucose homeostasis, so the observed phenomena could be responsible for hyperglycaemia associated with the suramin therapy.

The stimulatory action of this compound on glucose output might be due to a fall in lactate formation (Table 1) probably in consequence to the inhibition of one of the key glycolytic step in glucose metabolism. This notion is supported by a concomitant fall of the glucose utilization and lactate production in renal tubules incubated with glucose in the presence of 200 μM suramin. Although suramin was reported to inhibit lactate dehydrogenase in *Onchocera volvulus* and *Trypanosoma brucei brucei* (Walter and Schulz-Key, 1980) no decrease in the lactate production was observed in the presence of aspartate+glycerol+octanoate, alanine+glycerol+octanoate or pyruvate as glucose precursors in renal tubules (Table 1). As fatty acids repress glycolytic glucose metabolism (Bolon et al., 1997; Hue et al., 1988), the addition of octanoate to the incubation medium markedly decreases lactate production in the kidney-cortex tubules (Table 1). Thus, the octanoate action might explain no further inhibitory effect of suramin on glycolysis in renal tubules incubated with either aspartate+glycerol+octanoate or alanine+glycerol+octanoate (Table 2).

As concluded from suramin-induced changes in intracellular gluconeogenic/glycolytic intermediates in the rabbit kidney-cortex tubules (Fig. 2), a decrease in flux through pyruvate–phosphoenolpyruvate step resulting in an inhibition of glycolysis might be responsible for a stimulation of gluconeogenesis at the level of pyruvate–oxalacetate–phosphoenolpyruvate futile cycle. The data are in agreement with no suramin action on glucose production in the presence of pyruvate (Table 2), as this substrate bypasses the reaction catalyzed by pyruvate kinase. A fall in alanine production in tubules incubated with aspartate+glycerol is also in accordance with the above observation, a decrease in pyruvate formation might result in a diminished alanine aminotransferase activity. It is interesting that suramin does not have the same effect on glucose metabolism in rabbit hepatocytes. It is possible that pyruvate kinase activity in hepatocytes exerts much weaker control on the overall activity of glycolysis/gluconeogenesis than it does in kidney tubules.

The strongest evidence supporting the thesis, that in the rabbit kidney-cortex tubules glycolysis is diminished by suramin due to pyruvate kinase inhibition, comes from measurements of the effect of this compound on pyruvate kinase activity in the cytosolic fraction of the rabbit kidney cortex (Fig. 3). The inhibitory effect of suramin on pyruvate kinase might be ameliorated at lower phosphoenolpyruvate concentrations by increased intracellular levels of fructose-1,6-bisphosphate (Fig 3A and 3B), an allosteric activator of this enzyme (Irving and Williams, 1973). Thus, it is likely that suramin, known to permeate the cell membranes (Baghdiguian et al., 1996) and to accumulate in kidney to much larger extent than in liver and other tissues, (McNally et al., 2000), might cause an inhibition of glycolysis in the kidney cortex by the direct action on pyruvate kinase, so in consequence the glucose output is increased. Much less significant accumulation of suramin in liver in comparison with that in kidney (McNally et al., 2000) might be responsible for no suramin action on glucose metabolism in hepatocytes.

In summary, as kidneys are important contributors to the whole body glucose homeostasis (Gerich et al., 2001), suramin-induced stimulation of glucose formation in renal tubules might be responsible for hyperglycaemia observed in patients undergoing suramin treatment (Kaur et al., 2002 for review).

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