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Effects of Streptozotocin on the Molybdenum Hydroxylases Activities of the Rabbits and Guinea Pigs

Yousuf Abdulmalik Al-Tayib
Department of Biology, Faculty of Science,
Al-Taif University, P. O. Box 5700,
Al-Taif, Saudi Arabia

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Abstract. Effects of streptozotocin on the molybdenum hydroxylases, aldehyde oxidase and xanthine oxidase activities on some organs of the rabbits and guinea pigs were investigated. Rabbits and giunea pigs were treated with streptozotocin (65 mg/kg body weight) using a single intrapertitoneal injection. The food intake of treated rabbits was significantly lowered (P<0.005) on the second day of treatment. The levels of plasma glucose of treated rabbits were significantly decreased (P<0.05). No effect of streptozotcin on rabbits aldehyde oxidase activity was observed.

The guinea pigs treated with streptozotocin showed significant decreases in aldehyde oxidase activities of the tissues of duodenum (P<0.03), spleen (P<0.005) and brain (P<0.005) using 3-methylisoquinoline as a substrate. Although the activity of brain aldehyde oxidase from treated guinea pigs was increased significantly (P<0.05) using phthalazine as a substrate, these differ-ences in brain aldehyde oxidase activities suggested that the isoenzymes of aldehyde oxidase are involved in these interactions. Furthermore, the activity of duodenal xanthine oxidase from treated guinea pigs was lower significantly (P<0005) than the control animals. The present study revealed that the rabbits and guinea pigs molybdenum hydroxylases differ markedly in respect of their effects on streptozotocin.

***Keywords*:** Molybdenum hydroxylases, Aldehyde oxidase, Xanthine oxidase, Streptozotoicin.

Introduction

Aldehyde oxidase (aldehyde-oxygen oxidoreductase EC1.2.3.1) and xanthine oxidase (xanthine-oxygen oxidoreductase EC1.2.3.2) belong to a family of enzymes known as molybdenum hydroxylases [1, 2]. Aldehyde oxidase and xanthine oxidase are widely distributed in nature, being found in species as various as sea anemone and man [3, 4]. In addition to the microsomal cytochrome P450 system, the liver also contains the molybdenum hydroxylases, aldehyde oxidase and xanthine oxidase, which play a complementary role to the mixed function oxidases in drug metabolism [5-9]. Both of the mixed function oxidases and molybdenum hydroxylases are involved in the

metabolism of quinine (antimalarial agent), quinidine (antiarrhythmic drug) and famcilovir (antivairal drug) [6-8].

As well, molybdenum hydroxylases catalyze the oxidation of aldehyde, endogenous, and exogenous N-heterocyclic compounds [10, p.85]. Aldehyde oxidase is broadly distributed but the most important studies are carried out on the rabbit liver aldehyde oxidase [2], and hence it was considered that this enzyme may properly be catalyzed by the oxidation of a variety of heterocyclic substrates than that from other species [2, 11, 12]. Species variations in the activity of aldehyde oxidase and xanthine oxidase are well known. Highest aldehyde oxidase activity has been determined in rabbits, guinea pigs and baboons [13], whereas dog liver exihibts minimal enzyme activity [14]. Rats show marked variation in aldehyde oxidase activity [13, 15]. Further, the highest xanthine oxidase activity is found in dogs, rats and cats [16]. Little has been reported on the effect of diseases on molybdenum hydroxylases activity. In our previous study [17], the activities of hepatic, renal and jejunal aldehyde oxidase and xanthine oxidase were decreased during diabetic situation of guinea pigs which was induced by streptozotocin. Accordingly, this investigation was achieved to throw some light on the effects of streptozotocin on the activities of aldehyde oxidase and xanthine oxidase prepared from rabbits livers and guinea pigs tissues (lung, stomch, duodenum, spleen and brain) which may show as regards their responses.

Materials and Methods

Chemicals

Phthalazine and phenanthridine were supplied by the Aldrich Chemical Company (Gellingham, UK), 3-methylisoquinoline from ICN Pharmaceuticals Inc. (Irvine, CA) and xanthine was purchased from Sigma Chemical Company (Poole, UK).

Animals

Male Dunkin-Hartley guinea pigs (450-500g) and male New Zealand white rabbits (667-789g) were obtained from King Fahd Medical Research Center, Jeddah, Saudi Arabia.

The animals were housed in groups of three in an environmentally controlled room with a temperature of 24°C and on 12 hours dark-light cycle. Animals' food and water were offered *ad libitum* throughout the study period. Guinea pigs and rabbits were injected intraperitoneally (ip) with a single dose of 65mg/kg body weight streptozotocin solution (dissolved in 50 mM citrate buffer, pH 4.5). Control guinea pigs and rabbits were injected in parallel with a saline. Animals were killed 5 days after the injection of streptozotocin or a saline.

Determination of plasma glucose

Plasma glucose of guinea pigs and rabbits was determined spectrophotometrically according to the method explained by Trinder [18]. The oxidation of glucose is catalyzed

by glucose oxidase. The resultant hydrogen peroxide is oxidatively coupled with 4-amino-phenazone and phenol in the presence of peroxidase to yield a red quinoneimine dye, the concentration of which at 546 nm is proportional to the concentration of glucose.

Enzyme preparation

Guinea pigs and rabbits were killed by cervical dislocation. Different tissues (liver, lung, stomach, duodenum, spleen, brain) were collected, frozen in liquid nitrogen and then stored at -80°C. Partially purified aldehyde oxidase and xanthine oxidase were prepared from tissue homogenates from both control and treated animals following the methods described by Johnson *et al.* [11] and Al-Tayib [19]. Tissue was weighed, finely chopped and homogenized in 3 volumes of ice-cold isotonic KCl (0.154 M) containing 0.1 mM EDTA for 30 sec with a polytron homogenizer. The resulting suspension was heated on a water bath at 50-55°C for 15 min, immediately cooled to 10°C, then centrifuged at 20,000xg for 25 min at 4°C. Sufficient solid ammonium sulfate was added to the filtered supernatant to give 50% saturation with stirring for 15 min at 4°C followed by centrifugation at 3000 xg for 15 min. The precipitate was washed with distilled water, and dissolved in 4 ml of 0.1 mM EDTA. The partially purified enzyme was stored in a deep freeze at -80°C until used for spectrophotometric analyses.

Enzyme assays

Aldehyde oxidase catalyzes the oxidation of a wide range of aldehydes and N-heterocyclic compounds [13]. As a result of this wide specificity, enzyme activity is often monitored with different substrates. Aldehyde oxidase activity was estimated spectrophotometrically using the method reported by Johnson *et al.* [12], with phthalazine (1 mM) and 3-methylisoquinoline (1 mM) at 420 nm, while the oxidation rate of phenanthridine (50 µM) was determined at 322 nm.

Xanthine oxidase activity was evaluated with xanthine (50µM) at 295 nm as described by Johnson *et al.* and Beedham *et al.* [20, 21].

Test cuvette (1 cm path length)

0.5 ml optimized concentration of phthalazine or 3-methylisoquinoline.
0.5 ml 10^{-3}M potassium ferricyanide containing $7.8X10^{-4}$M EDTA.
1.9 ml $6.7X10^{-2}$M phosphate buffer pH7.
0.1 ml of appropriately diluted enzyme in a total cell volume of 3 ml.

Or:

0.5 ml optimized concentration of phenanthridine or xanthine.
2.4 ml $6.7X10^{-2}$M phosphate buffer pH7.
0.1 ml of appropriately diluted enzyme in a total cell volume of 3 ml.

Reference cuvette (1 cm path length)

As for the test cuvette with the exception of substrate, protein estimations were carried out using the biuret method [22].

Statistical analysis

The data presented in this report are expressed as mean ± SD, and comparisons between experimental and control rabbits and guinea pigs were made using a two-tailed student's t-test.

Results and Discussions

Effects of streprozotocin on rabbits

The data presented in Table 1 reveals that the plasma glucose levels of streptozotocin-treated rabbits were found to be significantly lower (P<0.05) than that observed in controls. These data are considered to be unlike the findings on other species such as rats and guinea pigs, which were also treated with the same dose of streptozotocin [17, 23]. As shown in Table 1, the food intake of treated rabbits was significantly decreased (P<0.005) on the second day of treatment and this result is similar to that recorded by some workers in rats [23]. Moreover, the food intake of treated rabbits had risen considerably (P<0.0005) by the fourth day.

Table 1. Daily food intake and plasma glucose of control and streptozotocin (ST) treated rabbits

Experimental group	Plasma glucose (mM)	Food intake (g)			
		Day 1	Day 2	Day 3	Day 4
Control (N=6)	8.5±0.8	40.8±2.1	44.5±2.2	N.D.	49.8±2.4
ST-treated (N=6)	7.4±1.1*	58.8±1.5***	29.7±7.9**	N.D.	62.8±5.1***

Values are given as means ± S.D., where (n) is the number of rabbits. Significant differences from matched control rabbits are indicated by * (P<0.05), ** (P<0.005), and *** (P<0.0005).
N.D.: Not Determined.

Rabbit aldehyde oxidase acativity

The specific activity of aldehyde oxidase prepared from the livers of control and streptozotocin-treated rabbits was determined spectrophotometrically using phthalazine, 3-methylisoquinoline and phenanthridine (Table 2). the activity of hepatic aldehyde oxidase with the several substrates showed no significant differences in the enzymatic activity of the liver from control and streptozotocin-treated rabbits.

These present results declared that streptozotcin has no effects on rabbit liver aldehyde activity, while the same dose of this compound caused a significant decrease as below as (P<0.01) in the activity of guinea pig aldehyde oxidase using phenanthridine as a substrate [17]. Therefore, these results are recorded assuredly the presence of species variations in hepatic aldehyde oxidase activity. This also was confirmed by previous studies [13, 24] which stated that the rabbit hepatic aldehyde oxidase was unlike to that of man. In addition, the rabbit enzyme was found to give no reaction with carbazeran, whereas the human liver enzyme was detected to be oxidized by this compound rapidly [13]. Moreover, it has been found that the rabbit enzyme converts N-phenylquinolinium chloride predominantly to the 2-quinolone, whereas N-phenyl-4-

quinolone was the major product regarding with the same enzyme from guinea pigs, marmosets, baboons and man [13, 24].

Table 2. Effects of streptozotocin (ST) on rabbit liver aldehyde oxidase

Specific activity * (µmol/min/mg protein)			
Substrate	**Control (N=6)**	**ST-treated(N=6)**	***P*<°**
Phthalazine	0.0349±0.0037	0.0316±0.0022	N.S.
3-Methylisoquinoline	0.0052±0.0002	0.0051±0.0006	N.S.
Phenanthridine	0.0138±0.0019	0.0133±0.0028	N.S.

* The values are given as means ± S.D.
for the number of exmined animals (N=6)
N.S. : Not Significant.

Effects of streptozotocin on the guinea pigs

Guinea pigs were made diabetic by the injection of streptozotocin. Table 3 shows that the levels of plasma glucose of streptozotocin-treated guinea pigs are significantly higher than those of matched controls. This result is similar to that reported previously [17].

Aldehyde oxidase and xanthine oxidase activity in the guinea pigs tissues

The specific activity of aldehyde oxidase extracted from lung, stomach, duodenum, spleen and brain were determined spectrophotometrically using phthalazine, 3-methylisoquinoline and phenanthridine as substrates. Table 4 declares that by using phthalazine, the activity of duodenum aldehyde oxidase was significantly lower ($P<0.005$) in diabetic animals. Furthermore, the same table shows that the activity of aldehyde oxidase extracted from brain of diabetic guinea pigs was increased significantly ($P<0.05$).

Table 3. Plasma glucose concerntration (mM) of control and streptozotocin-treated guinea pigs

Control (N=6)	**Treated (N=6)**	***P*<°**
10.1 ± 1.6	17.2 ± 2.8	0.005

Values are given as mean ± SD, where (N) is the number of guinea pigs.
°The statistical significance of differences between control and diabetic guinea pig values are obtained using a two-tailed students t-test.

However, no significant differences in lung, stomach and spleen aldehyde oxidase activity were observed in streptozocin-treated as compared to control animals. In addition, this investigation indicates that the activity of duodenal oxidase was higher than that of the lung of control guinea pigs for this substrate. Therefore, this was similar to values reported by Beedham *et al.* [3]. Using 3-methylisoquinoline as substrate, the activity of aldehyde oxidase in duodenum, spleen and brain of diabetic animals was significantly lowered ($P<0.03$, $P<0.005$ and $P<0.05$ respectively) than control ones (Table 5). Furthermore, the activity of aldehyde oxidase with phenanthridine was significantly lowered ($P<0.0005$) in duodenal diabetic animals as compared to control animals (Table 6).

On the other hand, xanthine oxidase activity in the lung and duedenum of control and streptozotocin-treated guinea pigs was obtinable using xanthine as a substrate (Table 7). The activity of this enzyme, extracted from duodenum of diabetic guinea pigs, was significantly decreased ($P<0.025$), whereas no significant differences in lung xanthine oxidase activity were observed in streptozotocin-treated as compered to control animals.

Table 4. Effects of streptozotocin (ST) treatment on guinea pig aldehyde oxidase activity using phthalazine as a substrate

Specific activity * (µmol/min/mg protein)			
Tissue	**Control (N=6)**	**ST- treated (N=6)**	***P*<°**
Lung	0.0210±0.005	0.0237±0.0034	N.S.
Stomach	0.0171±0.0051	0.0168±0.0036	N.S.
Duodenum	0.0271±0.007	0.0137±0.0046	0.005
Spleen	0.0121±0.0009	0.0128±0.0019	N.S.
Brain	0.0044±0.0096	0.0072±0.0018	0.05

N.S.: Not Significant.

Table 5. Effects of streptozotocin (ST) treatment on guinea pig aldehyde oxidase activity using 3-methylisoquinline as a substrate

Specific activity * (µmol/min/mg protein)			
Tissue	**Control (N=6)**	**ST- treated (N=6)**	***P*<°**
Lung	0.0139±0.0032	0.0145±0.003	N.S.
Stomach	0.009±0.0046	0.0085±0.0049	N.S.
Duodenum	0.0131±0.0031	0.0085±0.003	0.030
Spleen	0.0167±0.0031	0.0092±0.0004	0.005
Brain	0.0075±0.0021	0.0022±0.001	0.05

N.S.: Not Significant.

Table 6. Effects of streptozotocin (ST) treatment on guinea pig aldehyde oxidase activity using phenanthridine as a substrate

Specific activity * (µmol/min/mg protein)			
Tissue	**Control (N=6)**	**ST- treated (N=6)**	***P*<°**
Lung	0	0	
Stomach	0	0	
Duodenum	0.0062±0.0004	0.0034±0.0012	0.0005
Spleen	0	0	
Brain	0	0	

Table 7. Effects of streptozotocin (ST) treatment on guinea pig xanthine oxidase activity using xanthine as a substrate

Specific activity * (µmol/min/mg protein)			
Tissue	**Control (N=6)**	**ST- treated (N=6)**	***P*<°**
Lung	0.0018±0.0004	0.0016±0.0005	N.S.
Stomach	0	0	
Duodenum	0.0363±0.0033	0.0225±0.0094	0.025
Spleen	0	0	
Brain	0	0	

N.S.: Not Significant.

The data recorded in Tables 4, 5 and 6 showed three different effects occurred on aldehyde oxidase activity after treatment with streptozotocin, but one of these effects was exciting in relation with the activity of brain aldehyde oxidase which was increased using phthalazine as a substrate, whereas the activity of this enzyme was declined by using 3-methylisoquinoline as a substrate. Besides, by comparing these results, it can be observed that the only aldehyde oxidase prepared from duodenum was interacted with phenanthridine when used as a substrate, whereas no reaction with this substrate by using aldehyde oxidase of lung, stomach, spleen and brain. On the basis of these differences, the presence of isoenzymes of aldehyde oxidase could be postulated. Further support for this suggestion can be found in the work of other authors, [25-28], who reported the presence of isoenzymes of aldehyde oxidase in mice, rats, rabbits and man.

It has been detected that the activity of molybdenum hydroxylases, aldehyde oxidase and xanthine oxidase, were controlled by a number of factors such as genetic determinants, hormonal influences and induction [3, 12, 29]. Testosterone has been shown to induce both molybdenum hydroxylases, with mature male rats having approximately 60% more hepatic xanthine oxidase activity than immature male or female animals [3, 29]. Castration inhibits the increase in molybdenum hydroxylases associated with puberty with this effect being reversed upon administration of testostrone [27, 29]. Furthermore, the current study clearly indicates the presence of a relationship between streptozotocin effects and the decrease of aldehyde oxidase and xanthine oxidase activities particularly on guinea pigs, but possibly this relationship is through the pineal hormone, melatonin, as reported by Beedham *et al.* and Al-Tayib [21, 30].

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تأثيرات الإستريبتوزوتوسين على نشاط إنزيمات الموليبدينوم هيدروكسيليزز في الأرانب والقُبيعات

يوسف عبد الملك الطيب

قسم الأحياء، كلية العلوم، جامعة الطائف،

ص ب ٥٧٠٠، الطائف، المملكة العربية السعودية

(قدم للنشر في ١٤٢٥/٣/١٣هـ؛ وقبل للنشر في ١٤٢٥/١١/١٣هـ)

ملخص البحث. دُرست تأثيرات الإستريبتوزوتوسين على نشاط إنزيمات الموليبدينوم هيدروكسيليزز، الدهيد أُكسيديز والزنثين أُكسيديز، في بعض أعضاء الأرانب والقُبيعات (خنازير غينيا). عُولجت الأرانب والقُبيعات بمادة الإستريبتوزوتوسين (٦٥ ملغم/كغم من وزن الجسم) بواسطة حقنة واحدة في التجويف البطني. نتج عن هذه المعالجة انخفاض معنوي ($P<0.005$) في معدل الطعام المتناول من قبل الأرانب بعد مرور يومين من المعالجة كذلك لوحظ انخفاض معنوي لمستويات جلوكوز البلازما للأرانب المعالجة ($P<0.05$). لم يلاحظ أي تأثير للإستريبتوزوتوسين على نشاط إنزيم ألدهيد أُكسيديز في الأرانب.

نتج عن معالجة القُبيعات بالإستريبتوزوتوسين انخفاض معنوي في نشاط إنزيم ألدهيد أُكسيديز لأنسجة الإثنا عشريّ ($P<0.03$) والطحال ($P<0.005$) والمخ ($P<0.05$) وذلك بإستخدام ٣- ميثاليل ايزوكوينولين كحليلة يعمل عليها هذا الإنزيم. وبالرغم من ذلك، لوحظ زيادة معنوية ($P<0.05$) في نشاط إنزيم ألدهيد أُكسيديز المخي للقُبيعات المعالجة بالإستريبتوزوتوسين وذلك بإستخدام مادة الثلازين كحليلة لهذا الإنزيم. هذه الإختلافات في نشاط إنزيم ألدهيد أُكسيديز المخي للقُبيعات المعالجة تقترح وجود الصور المتعددة لهذا الإنزيم والتي لعبت دور في هذه التفاعلات. إضافة إلى ذلك، وجود انخفاض معنوي ($P<0.0005$) في نشاط إنزيم الزانثين أُكسيديز لأنسجة الإثنا عشريّ للقُبيعات المعالجة.

أوضحت الدراسة الحالية أن إنزيمات الموليبدينوم هيدروكسيليزز للأرانب والقُبيعات مختلفة بصورة واضحة فيما يتعلق بتأثير الإستريبتوزوتوسين على نشاط هذه الإنزيمات.