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Hypoglycemic Effects of *Atractylodis Rhizoma* in Rats with Streptozotocin-Induced Hyperglycemia

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ABSTRACT

A single i.v. dose of streptozotocin (65 mg/kg) given to rats has produced a marked hyperglycemia (>500 mg serum glucose/dl). Since the Atractylodis Rhizoma is known to have hypoglycemic action, the water extracts of Atractylodis Rhizoma (ARWE) was given to the streptozotocin-induced (SZ) hyperglycemic rats. To determine whether ARWE has the anti-hyperglycemic effects, two different daily doses of ARWE (i.e. 0.2 g/kg and 2.0 g/kg) were given orally to the SZ rats for up to 8 days. Thereupon, serum levels of glucose, insulin, amylase and cholesterol were determined on days 1, 3 and 8, following the initial and repeated daily administrations of ARWE.

On day 8, glycogen content and glucose-6-phosphatase activity in the liver were assayed. Results showed that ARWE decreased the serum glucose levels, which had been markedly elevated by the SZ pre-treatment.

In support of this, the serum insulin level, which had been quickly lowered by the SZ pre-treatment (20μU/ml), was quickly elevated in the ARWE dose dependent manner that, at 2.0 g/kg ARWE, the serum insulin level was increased (65μU/ml) above the normal level (42μU/ml).

Also, the serum amylase level, which was steadily decreasing after the SZ pre-treatment, was restored to the normal level folowing 8 day of ARWE (2.0 g/kg) treatment. Hepatic glycogen content and glucose-6-phosphatase activity, which decreased and increased, respectively in the SZ treatment group, were restored toward the normal level in SZ plus ARWE group.

Key Words: Streptozotocin-hyperglycemia, Atractylodis Rhizoma-hypoglycemia, insulin, rat

INTRODUCTION

It is well known that Atracylodis Rhizoma(Changchūl) is used mainly as a stomachic in Oriental medicine(Nogami *et al.*, 1985a; Nogami *et al.*, 1985b; Nogami *et al.*, 1986). *Atracylodes lancea* rhizomes is listed in the encyclopedia of Chinese medicine as an agent known to have hypoglycemic actions. *Atractylodes ovata* rhizomes(family Compositae) has been demonstrated to diminish blood sugar levels in rabbits(Li *et al.*, 1936). A water extract of *Atractylodes japonica* rhizomes(Baikchūl) was also shown to reduce the blood glucose level in normal mice. Three glycans from Atractylodis Rhizoma, such as the atractan a, b and c, were shown to have the hypoglycemic actions in the normal and alloxan-induced hyperglycemic mice(Konno *et al.*, 1985). However, we have as yet little information as to the nature of the hypoglycemic principle present in the rhizomes of *Atractylodes chinensis* Koidz.

Streptozotocin(SZ), a methylnitrosourea derivative of 2-deoxyglucose, has been shown to have diabetogenic effects by its toxic effect on beta cells of pancreas. Because of its well knwon diabetogenic effect, SZ is used widely as a model drug to induced the hyperglycemia in animal models(Dulin *et al.*, 1969; Like and Rossini, 1976; Bonner-Weir *et al.*, 1981; Wilson *et al.*, 1984).

Therefore, present study was designed to determine the mechanism of hypoglycemic activity of the water extract of *Atractylodes chinensis* rhizo-

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mes. The ARWE was given to the SZ-induced hyperglycemic rats and the time dependent changes of blood glucose and insulin levels along with other biochemical parameters have been determined.

MATERIALS AND METHODS

Experimental animals

Male Sprague-Dawley rats, weighing 180-200 g, at 8 weeks of age were used for all studies. Rats were given free access to a commercial pellet diet(Sam-Yang Combination Feed Co., Seoul, Korea). Streptozocin(Sigma chemical Co.) was injected via dorsal tail vein as a single dose(65 mg/kg, B.W.). 48 hour after the SZ injection, blood glucose levels were meausred and rats with more than 500 mg/dl serum glucose were chosen for this study. SZ was dissolved in an acidified saline solution just before injection. Rats were divided into 6 groups; 1) untreated normal group. 2) normal rats given 0.2 g/kg of ARWE for 7 day(AR-1). 3) normal rats given 2 g/kg of ARWE for 7 days(AR-2). 4) SZ control group. 5) SZ plus AR 1 group and 6) SZ plus AR2 group. Table 1 shows the experimental design for this study.

Preparation of ARWE

Atractylodes chinensis rhizomes were purchased from an Oriental medicine clinic in Chunchon, Kangwon-Do, Korea. 100 g of the rhizomes was extracted with 1 liter of deionized water by boiling for 6 hours under refluxing condition, total solution was filtered and evaporated in vacuum at 50 -60℃. It was again dried in vacuum dry oven at 40℃ for 24 hours. We have obtained 28 g yellow-brownish colored powder from 100 g of *Atractylodes chinensis* rhizomes.

Sampling of biological fluids

Blood was collected from paraorbital venous plexus with capillary tube at 10:00-11:00 a.m. on day 1,3 and 8 after treatment with ARWE. Serum was obtained by centrifuging at 1,000×g for 15 minutes. Before the total urine collection, the rats were transferred to metabolic cages for 24 hours, and urine was collected for glucose determination.

At day 8, rats were anesthetized by an intraperitoneal injection of pentobarbital and the abdominal cavity was opened. Liver was perfused with 0.15 M KCl and used for glycogen assay. Hepatic microsomes were prepared and used for glucose-6-phosphatase activity assays.

Chemical assays

Serum glucose levels were determined by the o-toluidine method(Hultman, 1959) and the serum insulin levels were measured by radioimmunoassay method(with autogammacounter, Peckard, U. S.A., No. 1000). Also, the serum amylase activity was analyzed by iodometric method(Caraway, 1959; Mc Nair, 1970) and the serum cholesterol level was assayed by the modified Parekh and Jungs method(Parekh and Jung, 1970). Urinary glucose level was determined by the Benedict's

Table 1. Experimental designs

Groups	No. of rats	Profiles of dose	Route of administration	Collection time and site of blood and urine	Liver assay
Normal control	6	non-treatment		Blood ; 10:00 – 11::00 a.m. on days, 0, 1, 3, and 8 Site : paraorbital venous plexus Urine ; 24 hour urine from metabolic cage	Sacrifice ; day 8 Assay ; glycogen and glucose-6-phosphatase activity
Normal + AR1	6	ARWE (0.2g/kg/day)	p.o.		
Normal + AR2	6	ARWE (2g/kg/day)	p.o.		
SZ control	6	SZ (65mg/kg)	i.v.		
SZ + AR1	6	SZ (65mg/kg) + ARWE (0.2g/kg/day)			
SZ + AR2	6	SZ (65mg/kg/day) + ARWE (2g/kg/day)			

A single i.v. dose of streptozotocin (65mg/kg) was injected, and after 48 hours, rats demonstrating marked hyperglycemia (> 500 mg/dl) were orally administered two respective doses (0.2, 2g/kg) of ARWE for 7 days.
AR : Atractylodis Rhizoma, ARWE : Atractylodis Rhizoma Water Extract. SZ : Streptozotocin.

method(Benedict, 1911).

Hepatic glycogen contents and glucose-6-phosphatase activity were determined according to the methods describd by Good *et al.*(1963) and Zakim *et al.*(1973), respectively.

Statistical analysis

Statistical analysis of the data was performed by Student's t-test. Significance was set at the 5% level.

RESULTS

Effect of ARWE on body weights

Figure 1a shows relative body weights were increased in all groups regardless of ARWE-treatment. At day 0 (pre-treatment of ARWE), body weight was decreased and this was assumed to be due to restraint in the metabolic cage. Figure 1b. shows rapid decrease of body weights by the SZ treatment. After the ARWE treatment, the SZ induced weight loss was inhibited and SZ plus AR1 group showed the smallest loss of body weight which were measured at days 1,3 and 8.

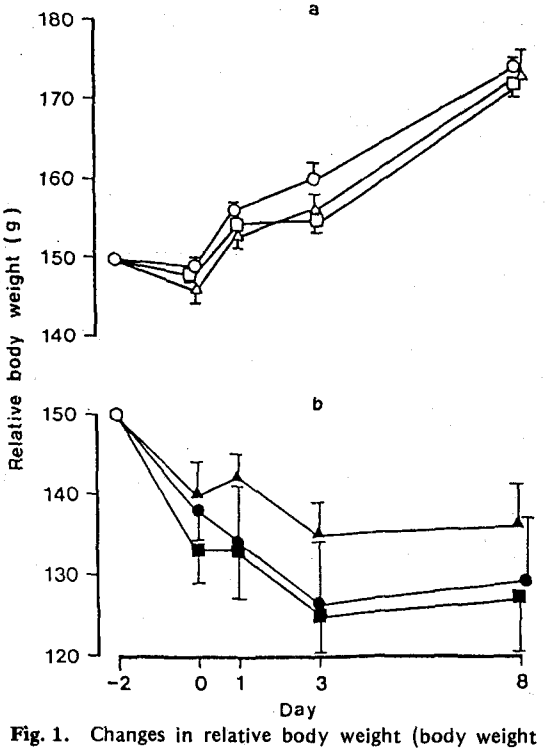

Fig. 1. Changes in relative body weight (body weight of each group as 150 g) after administration of Atractylodis Rhizoma Water Extract (ARWE) in normal (a) and streptozotocin (SZ)-induced hyperglycemic rats (b). SZ was injected via dorsal tail vein as a single dose (65 mg/kg). ARWE was administered after injection of SZ in 48 hours. Each value represents mean ± S.E. ○, ● : control group, △, ▲ : AR-1 group (0.2g/kg), □, ■ : AR2 group (2.0g/kg).

Effect of ARWE on serum glucose levels

Figure 2a shows that ARWE by itself did not have any influence on the serum glucose levels in the normal rats.

Figure 2b shows the marked increase of the serum glucose levels caused by the SZ injection. However, the SZ plus AR1 group and SZ plus AR2 group showed significant decrease in serum glucose levels. This occured in a dose dependent manner. The ARWE lowered the serum glucose levels in the SZ treated rats by 13.1%, 9.5%, and 36.3% at days1,3 and 8, respectively for the AR1 group. And for the AR2 group, by 19.1%, 22.9% and 42.9% on days of 1,3 and 8, respectively.

Effect of ARWE on serum insulin levels

Figure 3 shows that serum insulin levels were rapidly decreased by the SZ-induction and by 48 hours after the SZ treatment the serum insulin level was about 20μU/ml. The normal value was 42$\pm$ 4μU/ml. In the ARWE treated groups, serum insulin levels were significantly increased at days 1,3 and 8. ARWE elevated the serum insulin levels in SZ plus AR1 group by 61.9%, 126.7% and 67.1% on days of 1,3 and 8, respectively. And for the SZ plus AR2 group by 212.4%, 231.6% and 216.4%. Examinations of the serum insulin levels for the normal plus AR1 and normal plus AR2 groups were not carried out because of insignificant changes occured in the pilot experiments.

Effect of ARWE on serum cholesterol levels

Figure 4a shows that ARWE has temporary lowering action on serum cholesterol levels at days 1 and 3 by 25.3% and 17.2%, respectively.

Figure 4b shows the rapid increase of serum cholesterol levels caused by SZ treatment. However, in the ARWE treated groups, their levels were not increased. Compared with SZ control

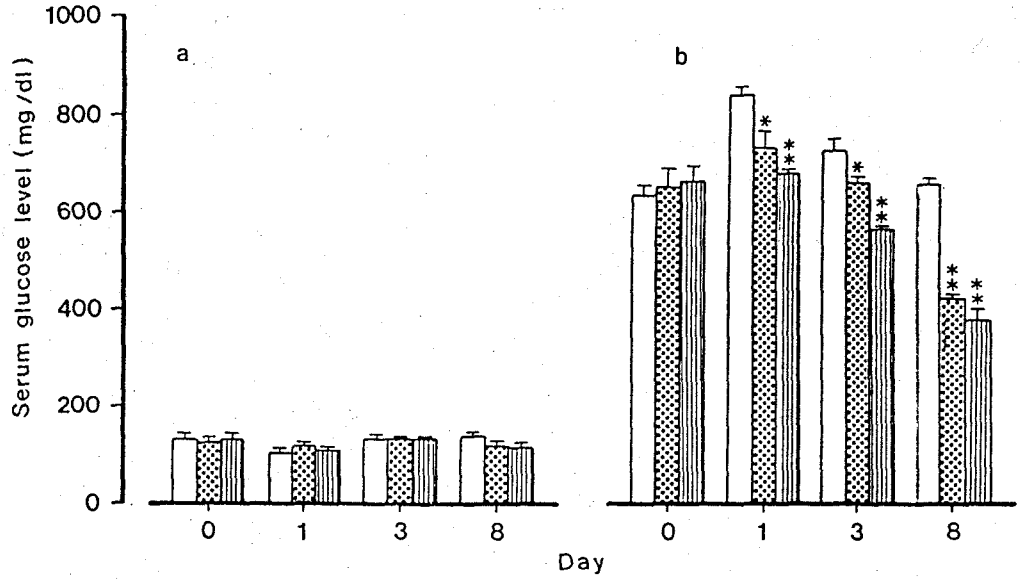

Fig. 2. Changes in serum glucose levels after administration of Atractylodis Rhizoma Water Extract (ARWE) in normal (a) and streptozotocin (SZ)-induced hyperglycemic rats (b). SZ was injected via dorsal tail vein as a single dose (65 mg/kg). ARWE was administered after injection of SZ in 48 hours. Each value represents mean ± S.E.
* $P < 0.05$, ** $P < 0.001$ compared with control value. □ : control group, ▨ : AR1 group (0.2g/kg), ▩ : AR2 group (2.0g/kg).

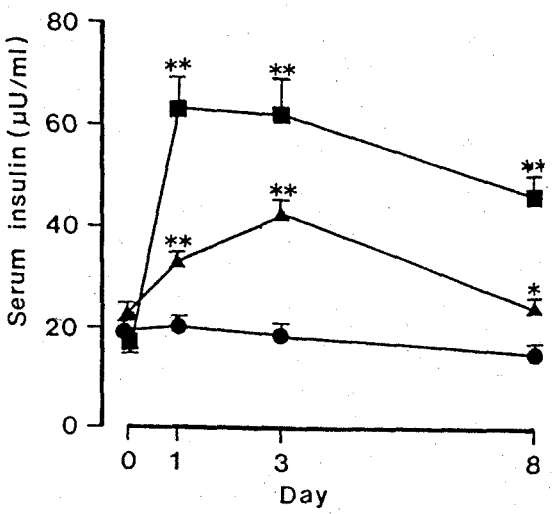

Fig. 3. Changes in serum insulin levels after administration of Atractylodis Rhizoma Water Extract (ARWE) in streptozotocin (SZ)-induced hyperglycemic rats. SZ was injected via dorsal tail vein as a single dose (65 mg/kg). ARWE was administered after injection of SZ in 48 hours. Each value represents mean± S. E.
* $P < 0.01$, ** $P < 0.001$ compared with control value. ● : control group, ▲ : AR1 group (0.2g/kg), ■ : AR2 group (2.0g/kg).

group, the srum cholesterol levels were lowered by 40.6%, 26.0% and 22.5% on days 1,3 and 8, respectively, in the SZ plus AR1 group. And for the SZ plus AR2 group, by 43.1%, 26.6% and 27.8%, respectively.

Effect of ARWE on serum amylase activities

Figure 5a shows that ARWE did not have any influence on serum amylase activities for normal rats.

Figure 5b shows that the serum amylase activities were decreased by SZ treatment. However, the ARWE treated groups showed significant recovery toward the normal value at day 8. When compared with the SZ control group, the serum amylase activities in the SZ plus AR1 and SZ plus AR2 groups were increased by 40.9% and 23.6% on days 3 and 8, respectively.

Effect of ARWE on urine volume

Figure 6a shows that ARWE treatment did not produce any effect of the urine volume for the normal rats. However, as shown as figure 6b, upon

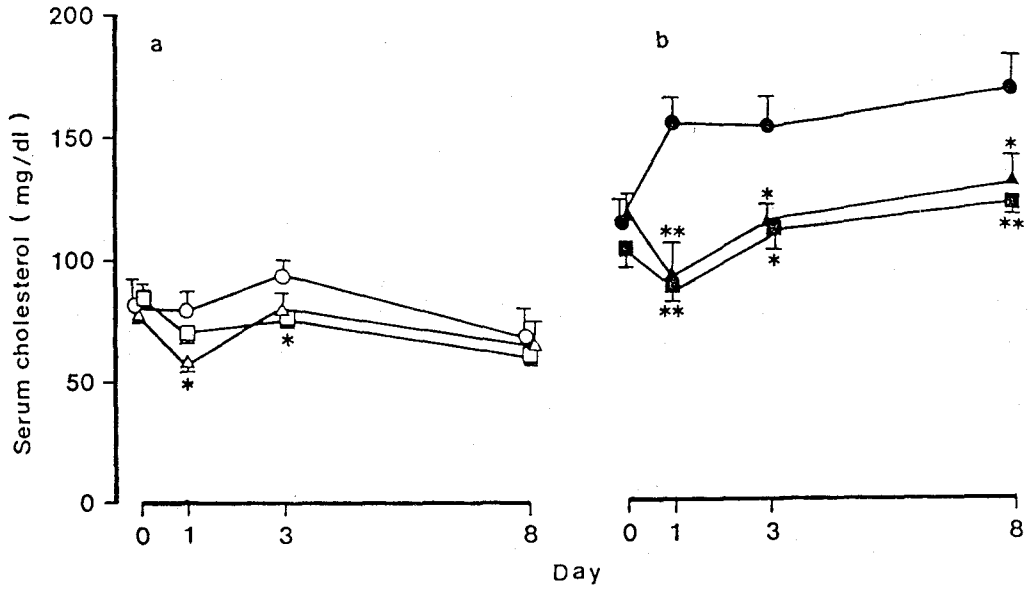

Fig. 4. Changes in serum total cholesterol levels after administration of Atractylodis Rhizoma Water Extract (ARWE) in normal (a) and streptozotocin (SZ)-induced hyperglycemic rats (b). SZ was injected via dorsal tail vein as a single dose (65 mg/kg). ARWE was administered after injection of SZ in 48 hours. Each value represents mean ± S.E. * $P < 0.05$, ** $P < 0.01$ compared with control value. ○, ● : control group, △, ▲ : AR1 group (0.2g/kg), □, ■ : AR2 group (2g/kg).

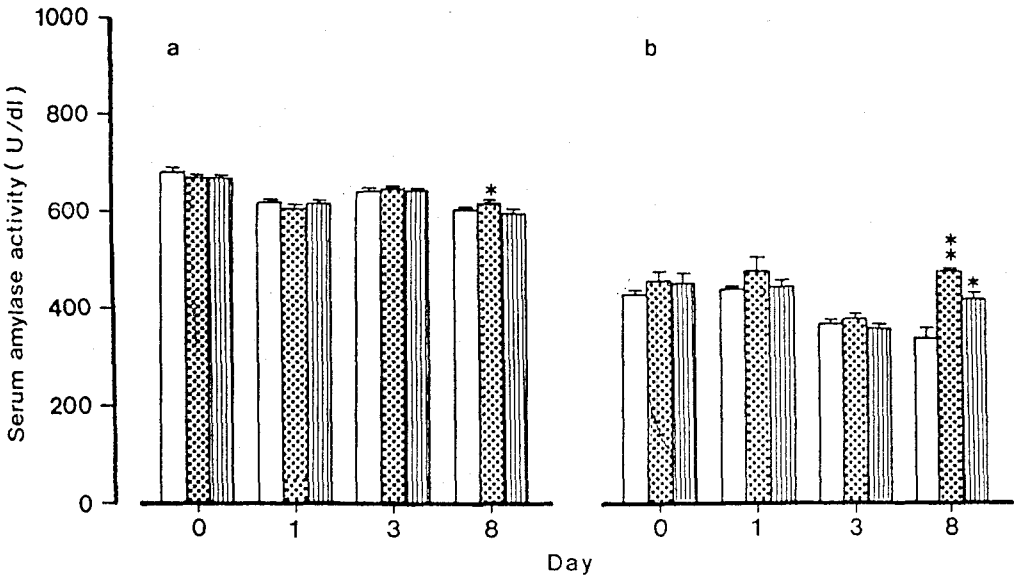

Fig. 5. Changes in serum amylase activities after administration of Atractylodis Rhizoma Water Extract (ARWE) in normal (a) and streptozotocin (SZ)-induced hyperglycemic rats (b). SZ was injected via dorsal tail vein as a single dose (65 mg/kg). ARWE was administered after injection of SZ in 48 hours. Each values represents mean ± S.E. * $P < 0.05$, ** $P < 0.01$ compared with control value. □ : control group ▨ : AR1 group (0.2 mg/kg), ▩ : AR2 group (2.0 g/kg).

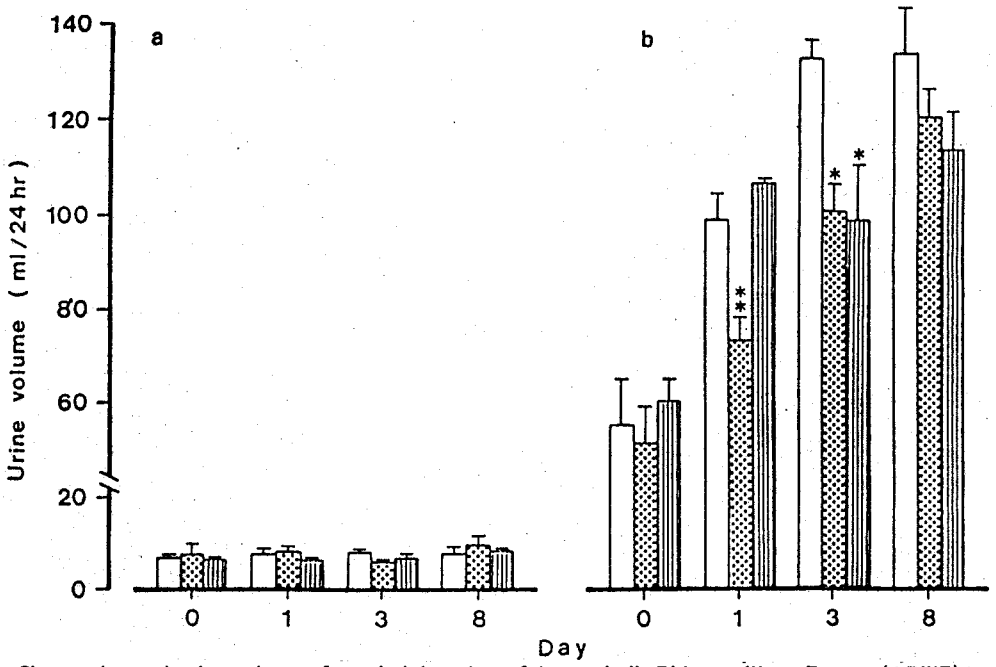

Fig. 6. Changes in total urine volume after administration of Atractylodis Rhizoma Water Extract (ARWE) in normal (a) and streptozotocin (SZ)-induced hyperglycemic rats (b). SZ was injected via dorsal tail vein as a single dose (65 mg/kg). ARWE was administered after injection of SZ in 48 hours. Each value represents mean ± S.E. * $P < 0.05$, ** $P < 0.01$ compared with control value. □ : control group, ▩ : AR 1 group (0.2 mg/kg), ■ : AR2 group (2.0g/kg).

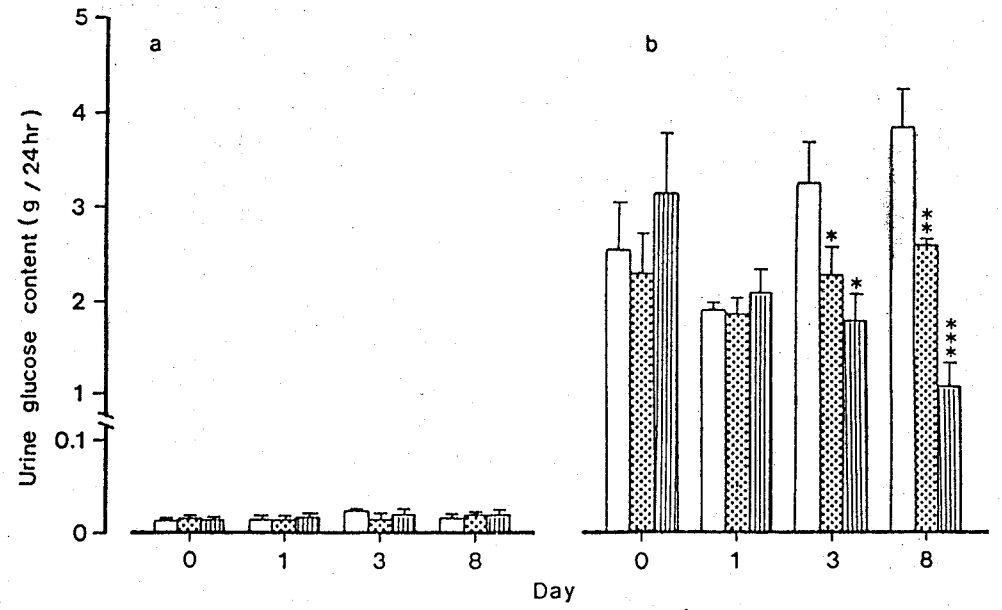

Fig. 7. Changes in urine glucose levels after administration of Atractylodis Rhizoma Water Extract (ARWE) in normal (a) and streptozotocin (SZ)-induced hyperglycemic rats (b). SZ was injected via dorsal tail vein as a single dose (65 mg/kg). ARWE was administered after injection of SZ in 48 hours. Each value represents mean ± S.E. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with control value. □ : control group, ▩ : AR1 group (0.2 g/kg), ■ : AR2 group (2.0 g/kg).

Table 2. Changes in liver glycogen levels and glucose-6-phosphatase activities after administration of atractylodis rhizoma water extract (ARWE) in normal and streptozotocin (SZ) induced hyperglycemic rats at day 8

Groups	Glycogen (mg/g wet weight)	Glucose-6-phosphatase (μmole/mg protein)
Normal	60.9 ± 5.9	5.49 ± 0.08
Normal + AR1	66.6 ± 3.7	5.52 ± 0.41
Normal + AR2	59.7 ± 5.5	4.79 ± 0.07
SZ	49.0 ± 4.9	7.46 ± 0.24
SZ + AR1	49.9 ± 0.2	6.77 ± 0.14*
SZ + AR2	54.1 ± 2.8	6.76 ± 0.04**

Each value represents mean ± S.E.
* : $P < 0.05$, ** : $P < 0.01$ compared with SZ control value.

induction of hyperglycemia by SZ treatment, the urine volume was marked increased. In the SZ plus AR1 group, urine volume was singificantly decreased toward normal value at days 1 and 3.

For the SZ plus AR2 group, significant decrease was observed only at day 3.

Effect of ARWE on urine glucose levels

Figure 7a shows that ARWE treatment by itself had no influence on urine glucose levels for the normal rats.

Figure 7b shows that the urine glucose level was highly increased, in proportion to increase observed with serum glucose levels, by the SZ treatment. However, in the SZ plus AR1 and SZ plus AR2 groups, the urine glucose levels were significantly decreased for the days 3 and 8.

Effect of ARWE on the liver glycogen level and glucose-6-phosphatase activity

ARWE did not have any significant influence on liver glycogen levels and glucose-6-phosphatase activities in the normal rats. SZ-treated rats showed significant decrease in glycogen level and increase in glucose-6-phosphatase activites. In SZ-treated rats, ARWE activities showed tendency to restore both glycogen level and glucose-6-phosphatase toward normal levels. This occured in a dose dependent manner (Table 2).

DISUSSION

Results showed that severe hyperglycemia developed 2 days after the intravenous injection of SZ(65 mg/kg).

The nonfasting diabetic state, characterized by polyuria, glycosuria, hyperglycemia, and hypoinsulinemia became evident. Rats were not fasted because the nonfasting blood glucose level correlatase with the pancreatic beta cell functions better than the fasting animals(Bonnevie-Nelson *et al.,* 1981). ARWE administration to the normal rats did not significantly influence the body weight, serum glucose, 24 hour urine volume and 24 hour uring glucose excretion. However, normal plus AR1 group and normal plus AR2 group showed only temporary reduction in serum cholesterol levels, and also temporary increase in serum amylase activity compared with those of normal control group. Also, the SZ injection produced a drastic impairment of growth. In any case, the lack of body weight gain in diabetes was shown to be caused by insulin deficiency, as the inhibited growth rate could be reversed by insulin administration (Otsuki and Williams, 1982). However, Feeding ARWE to rats after the SZ pretreatment did not shown the expected recovery of the body weights except the SZ plus AR1 group even though the serum insulin levels were increased markedly. This fact suggested that the body weight gain did not correlate with the increase of serum insulin level. In this study, the serum insulin levels were also dramatically reduced by the SZ injection and in the ARWE fed rats after the SZ pre-treatment showed, in a dose dependent manner, marked increase in the serum insulin level.

This may be due to the fact that ARWE alleviates SZ induced beta cell destruction, or ARWE stimulates the release of insulin from residual beta cells. In any case, we could not clearly explain the mechanism of the hypoglycemic action of ARWE in this study. Considering the results about a reduction of cholesterol levels by ARWE treatment in normal and SZ pre-treated rats, it may be suggested that ARWE did accelerate the lipid metabolism in normal and SZ-induced hyperglycemic rats. Increasing the dose of SZ results in increased severity of the diabetes(Junod *et al.,* 1969). As does alloxan, SZ has been shown to produce hyperlipidemia (Schein *et al.,* 1971; Schnatz *et al.,* 1971; Bar-On *et al.,* 1976). The

cholesterol metabolism is markedly altered in insulin-deficient, diabetic animals such as alloxan- or SZ-treated rats(Bar On *et al.*, 1976; Nervi *et al.*, 1974). Effects of SZ on exocrine pancreas may be due to insulin deficiency and exocrinal dysfunction reversed by exogenous insulin administration. It is possible, however, that some of the pancreatic abnormalities are due to alterations in nutritional and other hormonal state(Otsuki and Williams, 1982). Diabetic rats do not gain weight normally even though their food intake increased(De Castro and Balagura, 1975). In this study, it would be suggested that the rapid decrease in serum amylase activities after SZ pre-treatment was due to exocrine pancreatic dysfunction(Shin *et al.*, 1984). This results may be partly correlated with the loss of body weight with insulin. ARWE treated groups after SZ pre-treatment was slow in the recovery toward the normal value.

ARWE did not have any influence upon the 24 hours urine volume and glucose excretion in normal rats.

But, in SZ-induced hyperglycemic rats, ARWE treated groups showed the significat reduction in 24 hours urine volme and glucose excretion along with the serum glucose levels. The results indicted that ARWE did not have the hypoglycemic effect in normal rats. However, ARWE fed rats after SZ pre-treatment showed marked hypoglycemic action.

The effect of SZ on liver glycogen level and glucose-6-phosphatase activities is consistent with the result of Whiting *et al.*(1982). The effect of ARWE on liver glycogen and glucose-6-phosphatase activities in SZ treated rats is suggested to be the result of incresed insulin level induced by ARWE. The suggestion that insulin exerts a restraining effect on hepatic glucose output was made by Altszuler *et al.*(1976). It is suggested that decresed hepatic glucose output is responsible for the tendency of ARWE to restore glycogen level and glucose-6-phosphatase activities toward normal level, in SZ treated rats.

Therefore, we could suggest that a treatment of the herbal drug, the rhizomes of *Atractylodes chinensis* may improve a glucose metabolism by partly increasing serum insulin levels in SZ-induced hyperglycemic rats.

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═국문초록═

Streptozotocin에 의해 고혈당을 유발시킨 흰쥐에 미치는 *Atractylodis Rhizoma*의 영향에 관한 실험적 연구

한림대학 의학부 약리학교실

김 영 희, 송 동 근, 위 명 복

창출(*Atractylodis Rhizoma*)은 예로부터 건위목적으로 사용되어 온 생약중의 하나로서 실험동물에서는 혈당강하 작용이 있다고 알려져 있다. 그러므로 본 실험에서는 정상 및 streptozotocin (SZ)으로 고혈당을 유발시킨 흰쥐를 사용하여 *Atractylodes chinensis*의 수용성 추출물이 혈당에 미치는 영향을 단기간 관찰하여 다음과 같은 결과를 얻었다.

1. 정상 흰쥐에 창출의 수용성 추출물을 투여한 후 혈당치에는 영향을 미치지 않았으나 혈청 cholesterol치는 일시적인 감소를 나타내었다.
2. SZ로 고혈당을 유발시킨 흰쥐에 창출의 수용성 추출물을 투여한 후 1일, 3일 및 8일째는 용량 비례적으로 유의하게 혈당감소 및 혈중 insulin 농도의 증가를 나타내었다.
3. SZ 투여로 인한 cholesterol 수준의 증가는 창출의 수용성 추출물을 투여한 후 1일, 3일 및 8일째 억제되었으며, 8일째 감소되었던 혈청 amylase 활성도는 추출물 투여 후 정상 수준에 가깝게 회복되었다.
4. 24시간 뇨량 변화에서는 창출의 수용성 추출물 투여 후 1일 및 3일째 유의한 뇨량 감소를 나타내었고, 뇨당변화에서는 3일 및 8일째 혈당 감소와 비례하여 유의한 뇨당 감소를 보여 주었다.
5. SZ 투여로 인한 간장내 glycogen 함량의 감소 및 glucose-6-phosphatase 활성의 증가는 창출의 수용성추출물 투여로 정상수준에 가깝게 회복되었다.

이상의 결과들을 종합하면 창출의 수용성추출물은 정상 흰쥐의 당대사에는 영향을 미치지 않는 것으로 여겨지며, SZ로 고혈당을 유발시킨 흰쥐에 있어서는 혈당 조절의 중심적 역할을 하는 insulin 홀몬의 분비를 증가시켜 당대사를 촉진시킴으로서 혈당 강하 효과를 나타내었을 것으로 사료된다.