EFFECTS OF LIPOPOLYSACCHARIDE ADMINISTRATION ON GLUCOSE METABOLISM IN RATS

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Summary

In animals with sepsis or critical illness endotoxin exposure is accompanied by dramatic metabolic and hormonal changes. The effects of intraperitoneally lipopolysaccharide (LPS, 250 µg/kg in saline) treatment on blood glucose level and variations in insulin sensitivity were examined. The control group was injected i.p. (1 mg/kg) in 0.9% normal saline. Rats given LPS display no significant variations of blood glucose and a significant increase in insulin sensitivity. Taken together, our results demonstrate that endotoxemia could cause significant effects on glucose metabolism.

Keywords: lipopolysaccharide, glucose, insuline, Wistar rats

Introduction

In patients with sepsis, injury, or critical illness, profound and complex hormonal and metabolic changes are commonly observed which, on the whole, bring about an accelerated mobilization of protein, fat, and carbohydrates (Tessier et al., 2003). A hallmark of this hypermetabolic state is the fast appearance of a pronounced insulin resistance, especially with regard to carbohydrate metabolism (Chambrier et al., 2000). This insulin resistance affects the liver as well as skeletal muscle (Lang et al., 1990).

Lipopolysaccharide (LPS) levels in hepatic homogenate were firstly increased 1.5 hours following shock, and were higher than those in pulmonary and renal homogenates. LPS levels in pulmonary homogenate were also higher than those in renal tissue following shock. The liver is the most important organ for endotoxin accumulation after hemorrhagic shock for: 1) the portal circulation is the prominent route for endotoxin in the intestine to enter the body after hemorrhagic shock; 2) the liver is the largest organ that has monocyte/macrophage system, from where endotoxin is mainly eliminated out of the body (Vejchapipat et al., 2002).

Yelich and Janusek (1994) found that the administration of Salmonella enteritidis endotoxin to 10 day-old rats and 28 day-old rats at 2 and 30 mg/kg, respectively caused hyperglycemia as initial response to endotoxin followed by hypoglycemia. However, Kheir-Eldin et al. (2001) mentioned that the endotoxin elevated the blood sugar level. In contrast, Dhuley and Naik (1998) recorded that the LPS-induced decreases in blood sugar level in rats.

In the present study we examined the influence of systemic inflammation induced by bacterial lipopolysaccharide in rats, on blood glucose level and variations in insulin sensitivity.

Material and methods

Materials and drug administration

LPS from Escherichia coli serotype 0111:B4 and other reagents were obtained from Sigma-Aldrich (Germany). LPS (250 µg/kg, Sigma, Germany, dissolved in physiological saline 0.9% NaCl solution)
was intraperitoneally (i.p.) injected (1 ml/kg b.w.) once a day for 7 consecutive days.

**Animals**

20 male Wistar rats (3 month old) weighing 200 ± 50 g at the start of the experiment were used. The animals were housed in a temperature- and light-controlled room (22°C, a 12-h cycle starting at 08:00 h) and were fed and allowed to drink water *ad libitum*. The following groups of animals were used: (1) control group; (2) LPS-alone treated group. Rats were treated in accordance with the guidelines of Animal Bioethics from the Act on Animal Experimentation and Animal Health and Welfare Act from Romania and all procedures were in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). This study was approved by the local Ethic Committee and also, efforts were made to minimize animal suffering and to reduce the number of animal used.

**Blood Sampling Protocol**

On 7th day after LPS administration, blood samples were withdrawn via the Biotrol sampling catheter from 10 control and 10 LPS-treated rats. Blood samples (0.5 ml approximately/sample) were collected in vials containing EDTA for investigations.

**Glucose determination**

The whole blood was examined according to the Asatoor and King method (Hefco, 1977). Principle of the method consists of oxidation of glucose resulting molybdenum blue analyzed by 700 nm compared with controls. Standard curve was performed by replacing blood samples with the same volume of standard glucose concentrations 50, 100 and 200%. Using the standard curve, obtained extinctions were transformed into mg glucose/100 ml of blood.

**Statistical analyses**

Data were expressed as mean ± SEM. The data were analyzed statistically by means of the Student’s-t test. *P* values less than 0.05 were considered significant. Number of observation was 20.

**Results**

**Effects of LPS on blood glucose**

The glucose level in blood measured following LPS injection displayed no significant (*p*>0.05) variation after 7 days of injection in rats.

![Graph](image1.png)

**Figure 1.** Variations of blood glucose in LPS-treated rats compared to control. Values are means ± SEM (*n*=10 animals/group).

**Effects of LPS on insulin sensitivity**

Insulin was administered subcutaneously (0.125 UI/kg b.w.). Blood samples were withdrawn at 30, 60 and 120 minutes after insulin administration.

Insulin sensitivity increased to 30 minutes after dosing and then decreased significantly (*p*<0.01 at 60 and 120 minutes) in animals treated with LPS.

![Graph](image2.png)

**Figure 2.** Variations of blood glucose after 30, 60 and 120 minutes of insulin administration in LPS-treated rats compared to control. Values are means ± SEM (*n*=10 animals/group).
Discussion

The data obtained in this study indicated that endotoxins administration of *Escherichia coli* caused a non significant variation in glucose level and increase in insulin sensitivity at 30 minutes after insulin administration. Moreover, we observed that LPS caused hypoglycemia as an initial response followed by hyperglycemia. By contrast, Yelich and Janusek (1994) reported that endotoxin caused hyperglycemia as initial response followed by hypoglycemia.

In addition, bacterial endotoxins induced pancreatitis (Yamano *et al.*, 1998) which caused an increase in serum amylase associated with increase in glucose level. Moreover, it has been demonstrated that *in vivo* endotoxins treatment alter the ability of epinephrine to inhibit immunoreactive insulin secretion or to stimulate immunoreactive glucagon secretion (Yelich, 1993).

Conclusions

Our investigations have revealed that endotoxemia could potentially influence glucose metabolism. Also, we revealed an impairment of glucose utilization *in vivo* possibly by decrease of insulin sensitivity following by LPS treatment.

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References


