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Research Article

Correction of Insulin Resistance and Glucose Tolerance in Rats with Alloxan-Induced Diabetes Mellitus

Kozlova AP, Koroshchenko GA and Aizman RI*

Anatomy, Physiology and Life Safety, Novosibirsk State Pedagogical University, Novosibirsk, Russia

***Corresponding Author:** Aizman RI, Anatomy, Physiology and Life Safety, Novosibirsk State Pedagogical University, Novosibirsk, Russia.

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Abstract

Currently, diabetes mellitus (DM) has become one of the most common non-infectious pathologies, often causing complications in the cardiovascular system, kidneys, vision, nervous system, etc., which leads to early disability and mortality of people at the working age [1,2]. The constant increase in the cost of treatment of patients with this disease is a heavy burden on health care, so it becomes obvious that there is a need to find and develop facilities to reduce the prevalence of diabetes and its complications.

Keywords: Diabetes Mellitus; Correction of Insulin; Resistance and Glucose Tolerance

Introduction

For the study of DM, experimental models are of great importance, which can be used to test various methods of correcting carbohydrate metabolism and evaluate their effectiveness. Now, there are more than 30 known chemical compounds with diabetogenic properties that cause hyperglycemia of various genesis. Among them, alloxan presenting in the body tissues [3], that has a selective damaging effect on the beta-cells of the pancreas, and causes a model of DM. This alloxan model is widely used in experimental studies to find out the mechanisms of formation of diabetes mellitus and its correction using various means [4-6].

Considering that alloxan selectively destroys the β-cells of Langerhans islands by inducing reactions with free radicals, this model is closer to type 1 DM. However, it is known that alloxan-induced diabetes combines features of both types - 1 and 2 [7,8], characterizing by insulin resistance, which is clinically manifested by impaired glucose tolerance [9].

Impaired glucose tolerance has a dominant role in the pathogenesis of prediabetes, or latent diabetes [10]. This condition has no distinct clinical symptoms and is detected in 15 - 17% of cases by the results of a standard test of glucose tolerance during preventive examinations or accidentally. Very often, this hidden endocrine disorder leads to the development of DM [11], so timely diagnosis, as well as effective correction of this condition is an urgent task.

In recent years, in clinical practice, along with well-known drugs to reduce hyperglycemia in diabetic patients, began to actively introduce drugs of plant origin [12-14], the main effect of which is usually associated with the antioxidant action [12,15]. One of these widely advertised hypoglycemic drugs is turmeric (Curcuma longa) [6, 14], which has wide biological effects (antimicrobial [16], anti-inflammatory [17], antioxidant [15], hypolipidemic [18], etc. Recently, it was found that turmeric rhizome powder caused a decrease in glucose absorption in the digestive tract, increased the glycogenesis processes in the liver and muscles, activated insulin secretion and reduced the secretion of the counterinsular hormone - cortisol, which led to a decrease in hyperglycemia in rats with an experimental model of DM [19]. In this work, the aim was to study the effect of Curcuma longa rhizome powder on the sensitivity of tissues to the introduction of exogenous hormone (insulin resistance) and the degree of glucose uptake by tissues (glucose tolerance).

Materials and Methods

To achieve this goal, experiments were conducted on adult male Wistar rats. All animals were divided into four groups. The first (n = 10) and the second (n = 10) groups were control groups that consisted of intact animals. Animals of the third (n = 10) and the fourth (n = 10) groups were received a 10% alloxan solution at the volume of 0.1 ml/100 g body weight. Animals of the 1st and the 3rd groups were kept on a standard feed, while the the 2nd and the 4th groups of animals received additionally turmeric rhizome powder (Curcuma longa) - 2% of the feed weight. This amount of turmeric rhizome powder (Curcuma longa) corresponded approximately to 400 - 450 mg/rat per day depending on food intake, while the doses advised for human per day with meal were 1500 mg turmeric for 2 months [20]. Animals of all groups were kept in standard vivarium conditions, without restriction of water and food consumption.

To determine the effect of insulin on the concentration of glucose in the blood of rats insulin (Rosinsulin R, manufacturer - LLC "Plant Medsintez") was injected intraperitoneally at the rate of 2 IU per 1 kg. Before the injection of insulin, the background values

of glucose concentration were determined, and then this parameter was determined on the 1st, 2nd and 3rd hour of observation.

To evaluate the glucose tolerance, in the morning on an empty stomach, the background glucose concentration in the whole blood was measured and rats were given per os 30% glucose solution at the volume 5% of body weight. At the end of the 1st, 2nd and 3rd hour after solution intake the concentration of glucose in the blood was determined.

The concentration of glucose in the blood was measured by electrochemical enzymatic analysis on an automatic glucose analyzer Super GL (Dr. Muller, Germany).

Statistical analysis of the results was carried out based on calculating the arithmetic mean (M) and their errors (±m). Differences between indicators were evaluated using the Student's t-criterion for parametric samples and were considered significant at $p \leq 0.05$. Calculations were done using common formulas of standard programs of the Microsoft Office package.

All experiments were performed in accordance with International recommendations for conducting biomedical research involving animals, issued by the International Council for science (CIOMS) in 1985, with article XI of the Helsinki Declaration of the world medical Association (1964) and rules of laboratory practice in the Russian Federation (Order of the RF MOH dated 19.06. 2003, No. 267).

Results

After the injection of alloxan, the blood glucose concentration in the animals of the 3rd and the 4th experimental groups was significantly higher on the 1st day of observation than in the control, that indicated the development of DM (Table 1). However, during the entire observation period, the blood glucose level in animals that consumed turmeric with food was significantly lower compare to similar indicators of rats that consumed standard food, although it did not reach the control level.

Group N	Groups of animals	Back-ground	Days		
			1	3	6
1	Control	4,4 ± 0,3	3,6 ± 0,07	4,0 ± 0,2	4,4 ± 0,07
2	Control+ Curcuma	4,0 ± 0,3	3,5 ± 0,4	2,8 ± 0,3^{*+}	2,2 ± 0,2^{*+}
3	DM	5,0 ± 0,1	18,3 ± 0,2^{*+}	21,2 ± 0,1^{*+}	16,2 ± 0,3^{*+}
4	DM+Curcuma	4,2 ± 0,3	12,2 ± 0,06$^{*\Delta+}$	6,9 ± 0,2$^{*\Delta}$	5,3 ± 0,2$^{*\Delta}$

Table 1: Blood Glucose Concentration in Rats, mMol/l (M ± m).

Notes: (here and following): DM – diabetes mellitus; * - significant differences from similar parameters of control group (p≤0,05);

Δ – significant differences between experimental groups and the second one (p≤0,05).

+ - significant differences compared to the background values in each group (p ≤0.05)

It should be noted that while taking Curcuma longa rhizome powder in intact animals of the 2nd group, the blood sugar level on the 3rd and the 6th day of the experiment was also significantly lower than the similar indicators in the animals of the 1st group. Consequently, under the conditions of receiving Curcuma longa rhizome powder, rats with an alloxan model of DM had a less significant increase of glucose concentration in the blood and a faster its normalization.

At the next stage of the study, an insulin resistance test was performed, to check the sensitivity of tissues to the exogenous hormone injection.

In the healthy animals on standard feed, a significant decrease of glucose concentration in the blood during the 1st and the 2nd hours following the hormone injection was found, that indicated an adequate sensitivity of tissues to the hormone (Table 2). In the control group 1, by the 3rd hour of the experiment, the glucose concentration was restored to almost the background values, and in the group of healthy animals that consumed turmeric powder with food (group 2), the hypoglycemic effect on insulin administration was weaker, but persisted much longer. In the group of animals with the alloxan model of DM, whose diet included only standard food, there was no response to the injection of insulin in contrast to similar indicators of healthy animals. In rats with DM receiving

Group N	Groups of Animals	Back-Ground	Time After Injection, Hour		
			1	2	3
1	Control	4,1 ± 0,2	3,1 ± 0,3^{+}	3,2 ± 0,3^{+}	3,7 ± 0,4
2	Control+ Curcuma	5,5 ± 0,1	5,2 ± 0,1	5,1 ± 0,2	4,9 ± 0,2^{+}
3	DM	11,8 ± 2,7*	15,9 ± 3,2*	17,6 ± 2,4*	16,0 ± 2,8*
4	DM+Curcuma	10,9 ± 2,1*	10,0 ± 1,7*	8,7 ± 1,5 $^{\Delta+*}$	7,8 ± 1,5$^{\Delta+*}$

Table 2: Blood Glucose Concentration in Rats after the Insulin Injection, mMol/l (M ± m).

turmeric (group 4), a significant decrease in the glucose concentration following insulin injection was demonstrated on the 2nd and the 3rd hours.

Thus, turmeric rhizome powder increased the sensitivity of tissues to insulin in DM rats, that may explain one of the mechanisms of the hypoglycemic effect of the drug.

At the next stage, an oral glucose tolerance test was performed.

Blood Glucose Concentration in Rats after Intake of 30% Glucose Solution (5 ml / 100 g of body weight), mMol/l (M±m)

It can be seen (Table 3) that the background values of glucose concentration in the control groups were within the physiological norm, but in the group of animals with DM, both on standard feed and consuming turmeric, there was a statistically significant increase of glucose concentration in the blood compared with the control values. However, rats of the group 4, received turmeric powder had a significant lower increase of glucose concentration compare to animals on standard feed (group 3).

After the intake of 30% glucose solution the control group of rats demonstrated a slight but statistically significant increase of glucose concentration in the blood only during the first hour, which did not exceed the physiological norm. In this group, this indicator was restored almost to the background values already on the 2nd hour of observation. In group 2, there was no increase in the concentration of glucose in the blood, despite the sugar load. Along with this, in the groups with DM (3 and 4), the level of glucose in the blood after glucose load increased in the first hour and remained significantly higher for 2 hours in the 3rd group. In group 4, the glucose concentration increased also after the glucose solution intake, but significantly lower than in group 3. The presented data indicated an increase in the ability of tissues to deposit glucose under the influence of turmeric in both healthy animals and in DM.

Group N	Groups of animals	Back-ground	Time after intake, hour		
			1	2	3
1	Control	4,7 ± 0,3	6,0 ± 0,4+	5,3 ± 0,5	4,5 ± 0,4
2	Control+ Curcuma	4,3 ± 0,2	4,6 ± 0,2	4,4 ± 0,4	4,9 ± 0,4
3	DM	10,8 ± 0,8*	13,3 ± 0,9+*	14,1 ± 0,9+	10,8 ± 0,9*
4	DM+Curcuma	8,0 ± 0,8 Δ	11,2 ± 1,1+*	10,5 ± 1,5*	9,3 ± 0,9*

Table 3

Conclusion

Thus, turmeric has a fairly pronounced hypoglycemic effect both in healthy animals and under diabetes, which is due to increase of tissues sensitivity to the main hypoglycemic hormone - insulin, that causes an elevation of tolerance to excessive intake of carbohydrates.

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