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Original Contribution

POLOXAMER 407-INDUCED CHRONIC HYPERLIPIDEMIA IS NOT ASSOCIATED WITH DISORDERS OF BLOOD GLUCOSE LEVELS

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ABSTRACT

PURPOSE: The aim of the study was to evaluate the effects of chronic poloxamer 407 treatment on some parameters of lipid and glucose metabolism in a rat experimental model and to test the potential of this treatment to induce a condition similar to diabetes type 2. METHODS: The following parameters of lipid and glucose metabolism were measured: blood concentration of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, triglycerides and glucose concentrations following intravenous glucose tolerance test (IVGTT). Twelve male Wistar rats were used in the study. Rats were divided into two groups: 1) group C (control group) – rats from this group received no treatment during the entire experimental period; 2) group P (poloxamer group) – rats from this group were treated daily with poloxamer for a period of one month after which parameters of lipid and glucose metabolism were measured in both groups. RESULTS: Chronic poloxamer treatment induced significant changes in lipid metabolism parameters but did not affect glucose metabolism parameters. CONCLUSIONS: A 30 days experimental poloxamer treatment in rats is not associated with disorders of blood glucose levels.

Key words: Poloxamer 407, hyperlipidemia, glucose metabolism, diabetes type 2

INTRODUCTION

Poloxamer 407 is a copolymer consisting of polyethylene glycol and propylene glycol. It is a hydrophilic substance that is classified as a non-ionic surfactant. Poloxamer 407 has emulsifying properties, explaining its common application in increasing solubility of oily ingredients included in some cosmetic products and medications (1, 2). Poloxamer 407 is generally approved for use as an excipient in many pharmaceutical forms and is listed in the information sheet as an inactive ingredient in drug products like oral solutions, suspensions, and inhalation formulations. It also has reversible ability to form gels above a particular concentration and temperature, which makes poloxamer 407-based formulations potential systems for drug delivery (3, 4). There is an ongoing scientific research for using it as a removable support material in vascular surgery and bioprinting (5, 6). Although initially poloxamer molecules were considered to be biologically inert components, now there is growing evidence that some synthetic polymers can alter specific cellular responses (7). In spite of the reported low toxicity and good safety (8), poloxamer 407 has the potential to alter lipid profile and cause renal damage (2). For this reason, when administered in high doses, poloxamer 407 has become an important tool for developing various experimental animal models which are widely used today in biomedical research related to dyslipidemia and atherogenesis (9). Poloxamer 407 treatment allegedly increases blood levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, while reducing high-density lipoprotein (HDL) cholesterol levels (10). These changes in lipid profile are very similar to the dyslipidemic pattern observed in hyperlipidemia, which is a major risk factor for cardiovascular diseases, including atherosclerosis and coronary artery disease (11). Various *in vivo* studies using different animal species like rats, hamsters and mice have been conducted (12-14). Researchers have proposed various doses of poloxamer 407 for acute or chronic treatment of experimental animals. In small rodent animals it is administered intraperitoneally and all studies report consistent

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results – poloxamer 407 has a significant potential to induce hyperlipidemia (11). Furthermore, some studies indicate that multiple administrations of freshly prepared poloxamer-407 solution (10 mg/kg body weight once a day for 6 weeks) followed by an hour of fasting can induce diabetes (15, 16). In contrast, other studies have suggested that P-407 has no capacity to modulate either plasma insulin or blood glucose concentrations following administration to normal C57BL/6 mice (17). *In vivo* animal experimental models are still important in elucidating the etiology and pathogenesis of many disorders. Thus, the aim of the present study was to evaluate the effects of chronic poloxamer 407 treatment on some parameters of lipid and glucose metabolism in a rat experimental model and to test the potential of this treatment to induce a condition similar to diabetes type 2.

MATERIALS AND METHODS

Animals

Twelve male Wistar rats, aged 10-11 weeks, were used in the study. Rats were housed indoors at constant ambient temperature of 22 ± 2ºC, controlled humidity – 55 ± 10 %, 12:12 h light-dark photoperiod and had access to water and food ad libitum. All experimental procedures were in accordance with the ethical standards (Permit № 109/20.11.2014) of the Bulgarian Food Safety Agency).

Experimental design

Rats were divided into two equal groups – 1) group C (control group) – rats from this group received no treatment during the entire experimental period; 2) group P (poloxamer group) – rats from this group were treated with poloxamer – poloxamer 407 was administered intraperitoneally at a dose of 10 mg/kg of body weight daily for a period of one month (freshly prepared 1% solution of poloxamer 407 was used). At the end of the experimental period after overnight fasting blood samples were drawn from the tail vein for measuring the parameters of lipid profile and an IVGTT was conducted.

Laboratory parameters

Lipid profile parameters: total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides concentrations in serum were measured by spectrophotometric method (Kit Liquicolor, Human GMBH, Germany). VLDL cholesterol was calculated by the formula VLDL = triglycerides / 5.

Blood glucose: blood glucose concentrations were measured at the moment of sample collection by glucose-oxidase method using Glucometer Ellite /Bayer®/.

Intravenous glucose tolerance test (IVGTT)

The test started with measuring glucose blood levels – i.e. initial level. Immediately after that 40% glucose solution (0.125 ml/100 g of body weight) were infused in the tail vein over a period of 30 seconds. Blood samples were collected from the tail vein on 5^{th}, 30^{th}, 60^{th} and 120^{th} min after infusion. Glucose blood levels were measured at the moment of sample collection.

Statistical analysis

Results are presented as mean ± SD. Data was submitted to one-way ANOVA test and Tukey`s post hoc test (Graph Pad InStat3). Differences were considered statistically significant at the $p<0.05$ level.

RESULTS

At the end of the experimental period blood concentrations of total cholesterol increased significantly ($p<0.001$) in rats from poloxamer treated group (3.6 mmol/l) compared to control rats (1.63 mmol/l), **(Figure 1).**

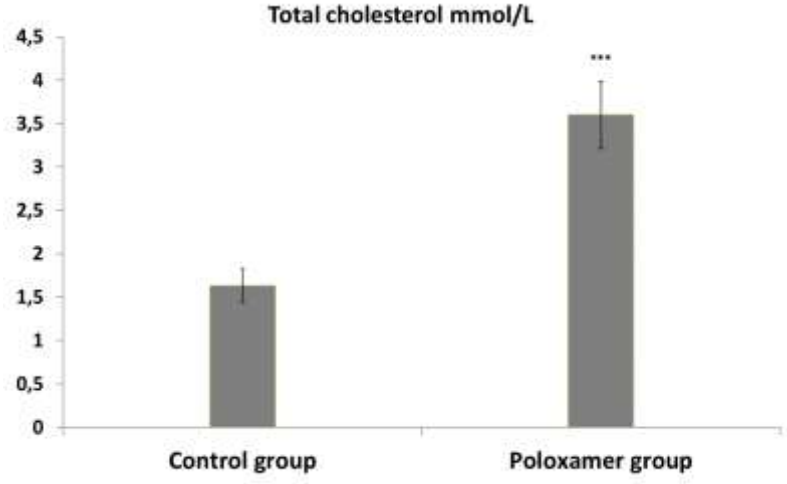

Figure 1. Total cholesterol levels in rats from control group (n=6) and rats from poloxamer group (n=6). Results are presented as mean ± SD. Statistically significant differences are indicated as follows: ******* $p<0.001$.

Rats treated chronically with poloxamer demonstrated a decrease in the concentrations of HDL cholesterol (0.22 mmol/l) as compared to control rats (0.27 mmol/l), but the decrease was not statistically significant **(Figure 2).**

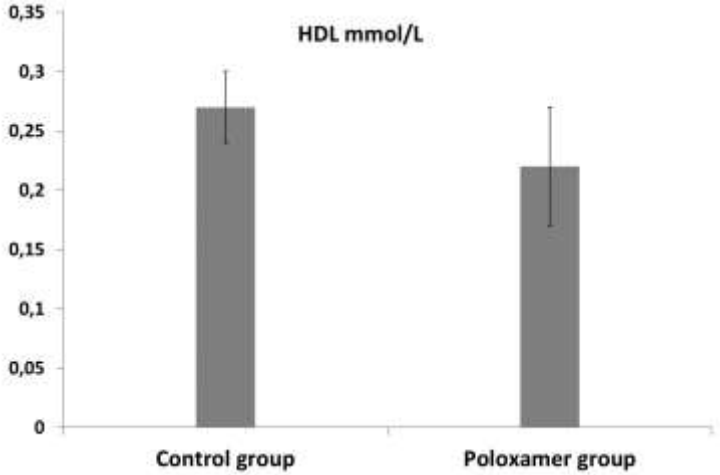

Figure 2. HDL cholesterol levels in rats from control group (n=6) and rats from poloxamer group (n=6). Results are presented as mean ± SD.

Logically, LDL cholesterol showed an increase in poloxamer group (2.92 mmol/l) as compared to control group (1.19 mmol/l), with the difference being statistically significant ($p<0.01$), **(Figure 3).**

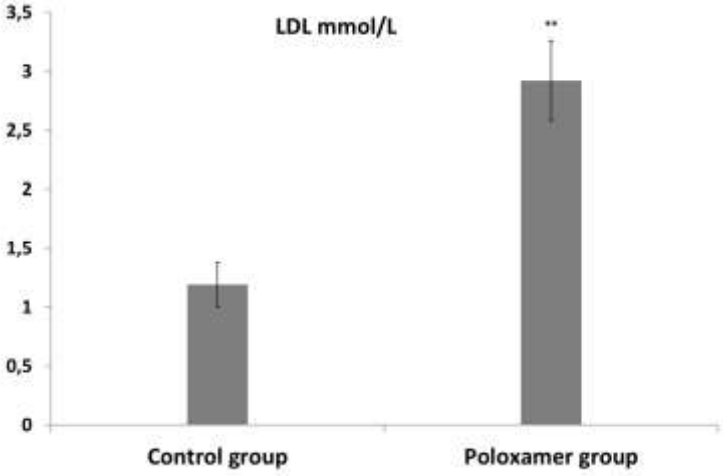

Figure 3. LDL cholesterol levels in rats from control group (n=6) and rats from poloxamer group (n=6). Results are presented as mean ± SD. Statistically significant differences are indicated as follows: ** $p<0.01$.

Poloxamer administration to experimental rats also led to a statistically significant increase ($p<0.001$) of VLDL cholesterol values – 1.05 mmol/l in experimental rats vs. 0.18 mmol/l in control rats **(Figure 4).**

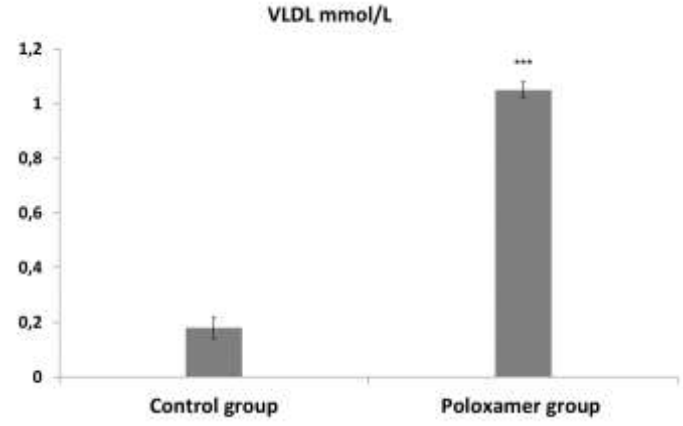

Figure 4. VLDL cholesterol levels in rats from control group (n=6) and rats from poloxamer group (n=6). Results are presented as mean ± SD. Statistically significant differences are indicated as follows: ******* $p<0.001$.

Almost identical were changes in triglycerides levels – 2.29 mmol/l in poloxamer treated group and respectively 0.43 mmol/l in control group, with the difference being statistically significant ($p<0.001$), **(Figure 5).**

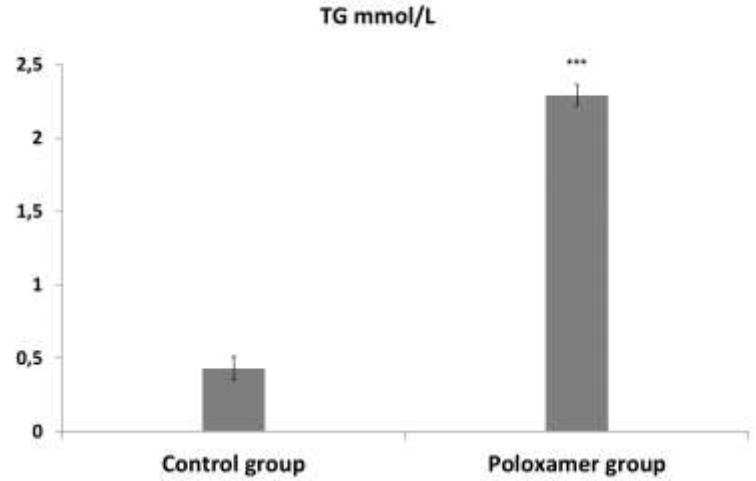

Figure 5. Triglycerides levels in rats from control group (n=6) and rats from poloxamer group (n=6). Results are presented as mean ± SD. Statistically significant differences are indicated as follows: ******* $p<0.001$.

During the intravenous glucose tolerance test blood glucose levels in poloxamer treated rats and control rats showed no significant differences. Initial blood glucose level was 5.45 mmol/l in control group and 6.45mmol/l in poloxamer group. Five minutes after the glucose infusion the values in the two groups were almost identical – 25.15 vs. 24.83 mmol/l. Blood glucose levels were also very similar on 60^{th} and 120^{th} minute after glucose infusion **(Figure 6).**

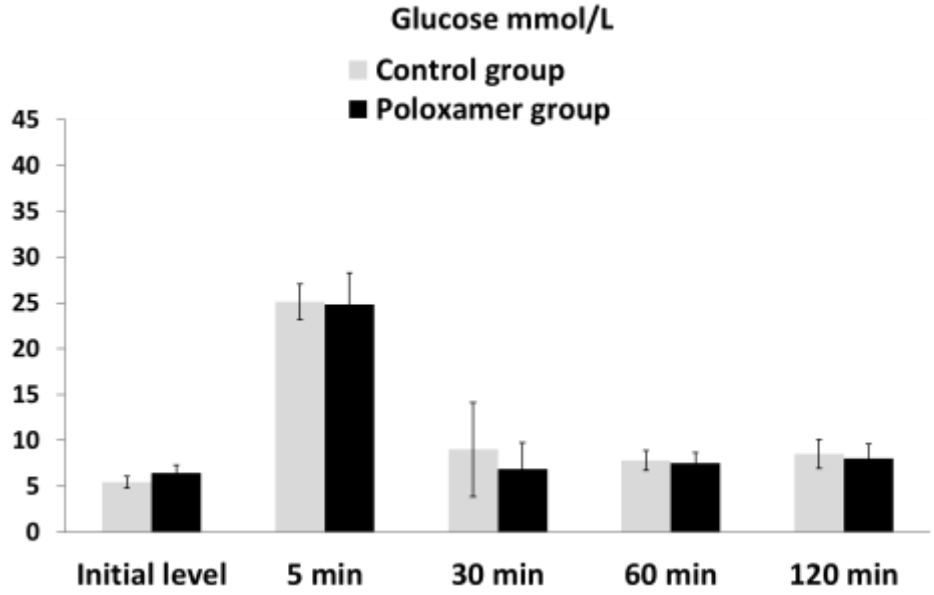

Figure 6. Glucose blood levels in rats from control group (n=6) and rats from poloxamer group (n=6) during IVGTT. Results are presented as mean ± SD.

DISCUSSION

The current study has demonstrated that chronic intraperitoneal treatment with poloxamer 407 induces hyperlipidemia of atherogenic profile in rats, but poloxamer itself and the resulting dyslipidemia have no effect on glucose homeostasis.

Numerous similar studies using experimental animals have evaluated the influence of poloxamer on lipid metabolism (11). Various routes, doses and periods of poloxamer administration have been described in these studies. For example, Korolenko et al. (2013) found that intraperitoneal administration of poloxamer 407 at a dose of 500 mg/kg twice per

week for 1 month can increase levels of triglycerides and total cholesterol in mice. According to this study, discontinuation of treatment does not resolve the dyslipidemia within the next five days, while after a single dose of poloxamer dyslipidemia resolves rapidly (18). Chronic treatment with poloxamer also leads to changes at the tissue level – early signs of atherosclerosis and liver steatosis have been reported (18, 19). Another study has used intravenous administration of poloxamer to rabbits in single doses of 5.5 mg/kg, 27.5 mg/kg and 137.5 mg/kg. Authors state that the resulting hyperlipidemia is dose dependent (20).

The pathogenesis of poloxamer induced hyperlipidemia has been investigated in many studies (21, 22). Poloxamer has been proven to have a dose-dependent inhibitory effect on plasma lipoprotein lipase, which leads to hypertriglyceridemia while the triglyceride production by the liver has minor contribution to the hyperlipidemia (21). Increased triglycerides levels following poloxamer injection return to baseline levels within several days, indicating that inhibition of lipoprotein lipase by poloxamer-407 is reversible or new enzyme is being produced to metabolize the triglycerides (22). According to some studies, apart from inhibiting lipoprotein lipase, poloxamer can also influence the expression of genes regulating hepatic synthesis of cholesterol (14). Increased cholesterol levels after poloxamer treatment are attributed to stimulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase) activity (an enzyme involved in production of cholesterol) and reduced LDL receptor expression in the cells that synthesize cholesterol (22, 14).

All of the findings discussed above, along with the results from our study, indicate that poloxamer 407 has the potential to induce hyperlipidemia. This statement is important for two reasons – (1) poloxamer is widely used in pharmaceutical and cosmetic formulations and potential risks should be seriously considered; and (2) poloxamer can be a useful tool for developing various animal models of metabolic disorders and diseases. In relation to the latter, Bharti et al. 2013, describe a model of diabetes type 2 induced by chronic administration of poloxamer 407 (15, 16). Unfortunately, these studies do not explain the mechanism of pathogenesis of diabetes type 2 induced by chronic poloxamer administration. A possible mechanism is lipotoxicity which causes cellular dysfunction and subsequent insulin resistance. Nevertheless, this model has not been reported to be used by other researchers and mechanisms of pathogenesis have not been explained. Moreover, review articles on experimental models of diabetes also lack information about this model. Our study failed to find any association between poloxamer induced chronic hyperlipidemia and disorders of blood glucose homeostasis. A possible reason for this is the shorter period of poloxamer treatment as compared to the previously mentioned studies (15, 16). Still, more research is needed to clarify the effects of poloxamer on carbohydrate metabolism.

CONCLUSIONS

Poloxamer 407 has the potential to induce significant changes in lipid metabolism and thus has become a useful tool for developing various animal models of hyperlipidemia and the resulting disorders and diseases. Further research is needed to evaluate any potential effects of poloxamer on glucose metabolism.

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Conflict of interests: The authors declare no conflict of interests.

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