Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 60; Numer/Number 4/2009
ISSN 0423–104X

Effect of opium on glucose metabolism and lipid profiles in rats with streptozotocin-induced diabetes

Wpływ opium na metabolizm glukozy i profil lipidowy u szczurów z cukrzycą wywołaną podaniem streptozotocyny

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Abstract

Background: This experimental study was performed to determine the impact of opium use on serum lipid profile and glucose metabolism in rats with streptozotocin-induced diabetes.
Material and methods: To determine the effect of opium, 20 male rats were divided into control (n = 10) and opium-treated (n = 10) groups. After diabetes induction, the animals were investigated for daily glucose measurements for 35 days. Serum lipid profile and haemoglobin A1c (HbA_{1c}) were assayed at the baseline (before induction of diabetes) and at 35-day follow-up.
Results: The glycaemia levels in the rats treated with opium were similar to the levels measured in the control rats (544.8 ± 62.2 mg/dl *v.* 524.6 ± 50.0 mg/dl, P = 0.434). In addition, there was no difference between the opium-treated rats and control rats in HbA_{1c} (6.5 ± 0.5% *v.* 6.6 ± 0.2%, P = 0.714). Compared to the control rats, the serum total cholesterol, high density lipoprotein (HDL), triglyceride and lipoprotein (a) in the test animals were similar.
Conclusion: Opium use has no significant effect on glucose metabolism and serum lipid profile in rats with induced diabetes.
(Pol J Endocrinol 2009; 60 (4): 258–262)

Key words: *opium, STZ-diabetic rats, glucose, lipid*

Streszczenie

Wstęp: To eksperymentalne badanie przeprowadzono w celu określenia wpływu stosowania opium na profil lipidowy i metabolizm glukozy u szczurów z cukrzycą wywołaną podaniem streptozotocyny.
Materiał i metody: Aby ocenić wpływ opium 20 samców podzielono na dwie grupy: kontrolną (n = 10) i otrzymującą opium (n = 10). Po wywołaniu cukrzycy przez 35 dni codziennie mierzono stężenie glukozy we krwi zwierząt. Profil lipidowy i odsetek hemoglobiny A1c (HbA_{1c}) określono na poczatku badania (przed wywołaniem cukrzycy) i w 35. dniu obserwacji.
Wyniki: Poziom glikemii u szczurów, którym podawano opium i w grupie kontrolnej był podobny (544,8 ± 62,2 mg/dl *v.* 524,6 ± 50,0 mg/dl, P = 0,434). Ponadto, nie stwierdzono różnic między grupą leczoną i kontrolną w zakresie wartości HbA_{1c} (6,5 ± 0,5% *v.* 6,6 ± 0,2%, P = 0,714). Również stężenia cholesterolu całkowitego, cholesterolu frakcji HDL, triglicerydów i lipoproteiny (a) były podobne w obu grupach.
Wnioski: Stosowanie opium nie ma istotnego wpływu na metabolizm glukozy i profil lipidowy u szczurów z eksperymentalnie wywołaną cukrzycą. **(Endokrynol Pol 2009; 60 (4): 258–262)**

Słowa kluczowe: *opium, szczury z cukrzycą streptozotocynową, glukoza, lipidy*

Introduction

More than 180 million people around the world have tried illegal drugs at least once. Of these people, 13.5 million are opium dependents. According to the U.N. World Drug Report for 2005, Iran has the highest proportion of opiate addicts in the world. It is estimated that about 4 million Iranians regularly or occasionally use opium, typically in the form of inhalation or oral intake [1–3]. Opium is commonly consumed throughout the nation, and after tobacco is the most widely abused substance in Iran. For centuries in Iran it was regarded as a privilege of the elderly, a largely medicinal comfort for pains, diarrhoea, insomnia, premature ejaculation, and worries accumulated over a lifetime of work and enjoyment [4–6]. However, it has been shown that opium abuse is a common problem among diabetic patients and is associated with severe depression and

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cigarette smoking [7]. Some of these problems arise from the conception of traditional medicine.

In two recent studies, the prevalence of opium consumption in patients with coronary artery disease was significantly higher in than the statistics in official reports from the general population of Iran [8, 9]. Opioid peptides, particularly enkephalins, may play an important role in a number of physiological and pathological conditions in the heart such as ischaemic preconditioning [IPC] via K+-ATP channel in cardiac mitochondria [10, 11]. It has been reported that diabetes is associated with a change of morphine antinociception and the development of tolerance or dependency to opioids. Hyperglycaemia in diabetes may alter hypothalamic-pituitary function, including the activity of the endogenous opiate system. These changes appear to modulate opioid antinociception and basal nociceptive processes [12, 13]. There are also several reports indicating that experimental diabetes mellitus attenuates the antinociceptive effect of morphine in animals [14, 15]. Recent clinical studies have reported controversial findings in terms of the effect of opium on serum electrolytes, lipid markers, and glucose metabolism [16, 17]. However, opium, opium alkaloids, and other alkaloids like quinine or Belladonna alkaloid agents were most widely used in Europe in the pre-insulin era as they were considered to have hypoglycaemic activity [18, 19]. To the best of our knowledge, there is little information on the effect of opium use in endocrine comorbidities in experimental models. Our study represents the direct quantification of the serum lipid profile and glucose metabolism in opium-treated rats after the induction of diabetes.

Material and methods

Animals, drug

Twenty male Sprague-Dawley rats weighing average of 250 ± 30 g were used in this study. The rats were transported to the Basic Research laboratory one week prior to the test day to allow acclimatisation and recovery from transport and handling. All animals were housed in an animal care facility under conditions of controlled light, 12 h light/dark, at 24 ± 1°C temperature and 55 ± 5% humidity, with standard chow diet and water available ad libitum. The investigation was approved by the institutional Review Board overseeing the participation of animal subjects in research at Tehran University of Medical Sciences, and the respective local government committee, which is advised by an independent ethics committee in our Cardiovascular Research Centre. This study conforms to the 'Guide for the Care and Use of Laboratory Animals' published by the US National Institute of Health (NIH publication No. 85–23, revised 1996). The experiments were carried out on two main diabetic groups: opium-treated (test group n = 10) and control (n = 10). The test rats received normal opium 20 mg dissolved in their 30 ml daily water intake, starting on the fifth day after induction of diabetes, for 30 days.

Induction of diabetes

Experimental diabetes was induced in all animals by a single dose injection of streptozotocin (STZ) (Zanosar, Pharmacia & Upjohn Company, Michigan, USA), 50 mg/kg intraperitoneally. Five days were allowed for destruction of pancreatic beta cells and development of Type 1 diabetes mellitus. Daily, the blood samples were collected and their glucose levels measured. The animals with blood glucose levels less than 300 mg/dL were not used in the study.

Blood sampling and laboratory assessments

Blood samples for glucose measurements were obtained by tail tip removal technique (Institutional Animal Care and Use Committee Guideline 9, 1999). In a sterile situation, a transverse section was made through the long axis of the tail 2 mm from the tip. After blood sampling, direct pressure was applied to the incision for 1–3 minutes to facilitate haemostasis. Repeated blood sampling was obtained by removing the clot. The blood glucose was measured daily by Accu-Check glucometer (Roche Diagnostics GmbH, D-68298 Mannheim, Germany) qualified in the Quality Control Department.

On the first and last days of the experiment, each rat received general anaesthesia by ketamine (50 mg/kg, *i.p.*) and lidocaine (5 mg/kg, *i.p.*) to obtain intracardiac blood collection (Intracardiac Blood Collection in Mice and Rats, Canadian Council Animal Care Guide regarding the Care and Use of Experimental Animals, 2008). In the ventral midline approach, a 2 cc syringe needle with 25 gauge needle was introduced just to the left of the base of the animal's sternum towards the heart at an angle of approximately 20–30°. After full collection of the blood sample, we safely removed and discarded the needle. The blood samples were used to measure haemoglobin A1C (HbA_{1c}), lipoprotein a (LPa), total cholesterol, triglyceride, and high density lipoprotein (HDL). HbA_{1c} was measured by using a bench top NycoCard® HbA_{1c} Reader II (Oslo, Norway) certified by the National Glycohaemoglobin Standardization Program, USA, September 2008. Serum levels of total cholesterol, triglyceride, HDL, and LPa were assayed using commercially available enzymatic kits (Pars Azmoon, Tehran, Iran), cholesterol and triglyceride using enzymatic colorimetric tests, HDL by precipitation of the apolipoprotein B100 containing lipoproteins with phosphotungstic acid, and LPa by immunoturbidimetric assay.

Table I. *Lipid profiles and glucose marker of the streptozotocin-diabetic rats (n = 20)*

Tabela I. *Profil lipidowy i wskaźniki stężenia glukozy u szczurów, którym podano streptozoocynę (n = 20)*

	Opium-treated (n = 10)	Control (n = 10)	*p* value
Baseline			
Glucose [mg/dL^{-1}]	112.2 ± 15.8 **	108.2 ± 15.9 *	0.579
HbA_{1c} (%)	2.6 ± 0.2 **	2.6 ± 0.3	0.451
Triglyceride [mg/dL^{-1}]	99.1 ± 8.5 **	96.9 ± 11.3 *	0.629
Total Cholesterol [mg/dL^{-1}]	107.7 ± 10.7 **	102.9 ± 11.9	0.356
HDL [mg/dL^{-1}]	42.1 ± 4.9	40.5 ± 3.9	0.430
LPa [mg/dL^{-1}]	6.8 ± 1.9	6.9 ± 1.4	0.895
35-day follow-up			
Glucose [mg/dL^{-1}]	544.8 ± 62.2 **	524.6 ± 50.0 *	0.434
HbA_{1c} (%)	6.5 ± 0.5 **	6.6 ± 0.2 *	0.714
Triglyceride [mg/dL^{-1}]	105.1 ± 4.8 **	102.9 ± 8.0 *	0.467
Total Cholesterol [mg/dL^{-1}]	113.5 ± 13.4 **	106.5 ± 15.0	0.287
HDL [mg/dL^{-1}]	40.5 ± 3.7	39.8 ± 2.8	0.632
LPa [mg/dL^{-1}]	6.5 ± 1.4	7.3 ± 0.9	0.158

Abbreviations: HbA_{1c}, haemoglobin A1c; [LPa], lipoprotein a; HDL, high density lipoprotein; *p values were < 0.05 and based on a paired *t* test to compare data of baseline and 35-day follow-up within control rats; **p values were < 0.05 and based on a paired *t* test to compare data of baseline and 35-day follow-up within opium-treated rats

At the end of the experiments, all the animals were sacrificed using an i.p. injection of 100 mg/kg sodium thiopental.

Statistical analysis

Data from the baseline and the last day were expressed as mean ± SD and were analysed by using Student *t* test and paired *t* test to compare before and after intervention levels of favorable parameters in each group. Modelling the mean glucose over time was the main feature of analysis that we followed to deal with the longitudinal data during the 35-day experiment. We performed general linear model repeated measures analysis to compare the concentrations of glucose across the two groups (*i.e.*, groups-by-time interaction). If the sphericity assumption was not satisfied (Mauchly's test of sphericity, $p \leq 0.05$), the Greenhouse-Geisser correction was reported. All statistical analyses were performed using Statistical Package for Social Science version 15 (SPSS Inc., Chicago, IL, USA). Probability values of $P < 0.05$ were considered statistically significant.

Results

The data of serum lipid profile, glucose, and HbA1c at the baseline and on the last day of 35-day follow-up are shown in Table I. Total cholesterol, LPa, triglyceride, and HDL showed no significant differences between the control and opium-treated animals. In both control and opium-treated rats, levels of triglyceride and were significantly increased from the baseline to the last day; 96.9 ± 11.3 mg/dL *v.* 102.9 ± 8.0 mg/dL, $p = 0.015$ and 99.1 ± 8.5 mg/dL *v.* 105.1 ± 4.8 mg/dL, $p = 0.028$, respectively. In the opium-treated rats, the increase of total cholesterol was also evident in a comparison between the baseline and follow-up data [107.7 ± 10.7 mg/dL *v.* 113.5 ± 13.4 mg/dL, $p = 0.016$].

In both groups, serum glucose was significantly increased on day 3 of diabetes induction and reached above 500 mg/dL within 5 days. Serum glucose between the groups was not significantly different at any time during 35-day follow-up. There was no significant interaction of group × time in repeated measure analysis [Fig. 1, $F = 1.310$, $p = 0.240$].

Discussion

Our main objectives were to evaluate the effects of available opium substance on glucose and lipid metabolism in STZ-diabetic rats. Here, the tested opium was a mixture of about 50 different samples. Crude opium contains the juice of the seed capsule of the opium poppy *Papaver sotnniferum*. The available substance was the dry, sticky or crumbly dark mass that is known as *raw opium* [20]. The major constituents of crude opium are morphine (approximately 10% by weight), noscapine (approximately 6%), papaverine (approximately 1%), codeine (approximately 0.5%) and thebaine (approximately 0.2%). However, the available substance may contain other constituents. The results of this experimental study demonstrated that opium, as an accessible substance which is generally used by Iranian addicts, has no effect on glucose metabolism or lipid profiles in rats with STZ-induced diabetes. Although the lipid indices were significantly increased after diabetes induction, no rats developed dyslipidaemia. This result

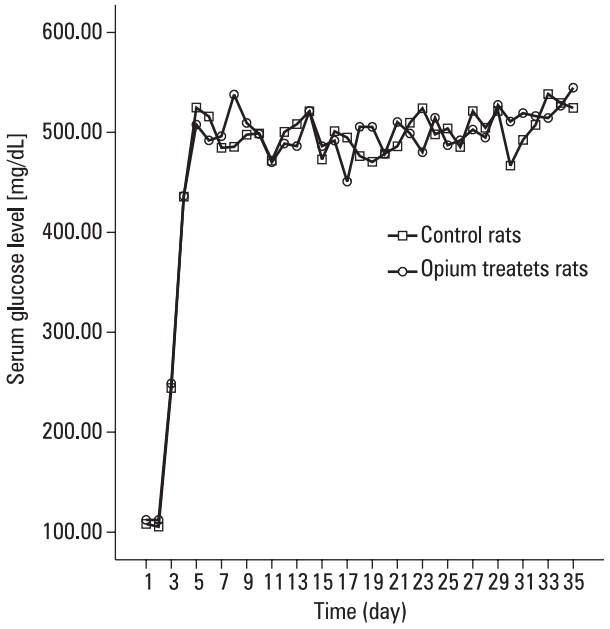

Figure 1. *Estimated marginal means of serum glucose level [mg/dL] in rats with induced diabetes comparing the opium-treated and control groups; Greenhouse-Geisser test, p = 0.240*

Rycina 1. *Oszacowane średnie brzegowe stężeń glukozy w surowicy [mg/dl] szczurów z wywołaną doświadczalnie cukrzycą w porównaniu ze zwierzętami leczonymi opium i z grupą kontrolną; test Greenhouse'a-Geissera, p = 0,240*

is consistent with some earlier studies. Azod et al. [16] showed that while opium use may decrease blood glucose temporarily in patients with type 2 diabetes, it had no clear long-term effects on blood glucose and HbA_{1c}. Karam et al. reported that addicted males with noninsulin-dependent diabetes mellitus had higher levels of HbA_{1c}, but lower levels of serum total protein and HDL. Cholesterol tends to be lower in diabetic addicted males, while HbA1c in addicted females was higher compared to non-addicted diabetics. Therefore, it was suggested that smoking opium increases serum glucose and decreases HDL, and thus adds to metabolic disorders in diabetic patients [17].

Some others have shown impaired glucose metabolism in opiate users. Ceriello et al. [21] found that plasma glucose and insulin responses in heroin and methadone addicts were altered according to oral and intravenous glucose load; the phenomena were linked to a reduced insulin response. In another study by Passariello et al. [22] the heroin users had a significant rise in plasma glucose concentrations following oral sugar, which persisted until the end of the study, and a significant decrease in insulin response. Moreover, the inhibitory effect of glucose on glucagon concentration was less evident in addicts compared with controls. Opiate addiction may produce a beta-cell dysfunction and, contemporaneously, a state of hyperinsulinaemia. A change in the rate of hepatic extraction of insulin and lower glucose disappearance rate has been reported in heroin addicts [23–25]. The finding of beta-endorphin and enkephalin in the human pancreas may suggest the direct effect of exogenous opiates on beta cell function [24, 26, 27].

Insulin and glucagon release from monolayer pancreatic islet cell cultures are inhibited in a dose-response fashion by various enkephalins. Morphine, however, stimulates insulin and glucagon release [28]. The effects of opioids on glucose homeostasis may not depend only on insulin. An activation of opioid receptors by either exogenous beta-endorphin or chemical agents, such as loperamide and tramadol, has been shown [29–31]. Tzeng et al. [30] found that loperamide, a selective agonist of opioid μ-receptor has the ability to increase glucose utilization and/or reduce hepatic gluconeogenesis in the liver of STZ-diabetic rats. It was hypothesized that loperamide enhances glucose uptake via an effect on the gene expression of glucose transporter 4 [GLUT-4] in skeletal muscle [32]. Moreover, this agent reversed the elevated mRNA and protein levels of phosphoenolpyruvate carboxykinase [PEPCK] in the liver of STZ-diabetic rats to near normal levels [30]. Therefore, it may modulate glucose homeostasis in diabetic rats without the presence of insulin. Insulin deficiency is clearly associated with changes in hepatic metabolism, including increased expression of PEPCK, which is a key enzyme of hepatic carbohydrate metabolism [33]. Decreased expression of skeletal muscle GLUT 4 was proposed previously to mediate the reduction of insulin-mediated glucose uptake into skeletal muscle in diabetes [34]. There is evidence that there is bidirectional cross-talk between the endogenous opioid system and glucose metabolism. Hyperglycaemia is associated with analgesia in rats and this hyperglycaemia-induced analgesia could be blocked by antagonists of opioids receptors [35]. The interaction between glucose and the opioid system is also supported by the report indicating diabetic and non-diabetic rats responded differently to the suppressive effect of naloxone on feeding [36].

Morley et al. [37] indicated that morphine addiction in rats was accompanied by an increase in brain levels of somatostatin, cholecystokinin, neurotensin, and substance P, and that naloxone-induced withdrawal decreased brain concentrations of TRH, somatostatin, neurotensin, and substance P. The expression of beta-endorphin sensitive receptor on skeletal muscle is vastly increased in type 1 and type 2 diabetic animals [38]. In other aspects, high plasma levels of [Met5]-enkephalin [39] have been reported in patients with diabetes, whereas Vermes et al. [40] observed normal levels of β-endorphin in diabetic patients; however, Cheung and

Tang [41] observed a decrease in β-endorphin levels in the rat neuro-intermediate pituitary compared to elevated levels in the anterior pituitary. Nevertheless, the controversies in current evidence assessed the interaction of opioids and endocrine system originates from different methodological strategies. Thus, further investigation is needed to assess the specific roles of the different opioid peptides and/or the mixture of exogenous opiates in the level of activation of opioid receptors related to the glucose-modifying pathways.

Conclusions

In conclusion, it is suggested that chronic opium use appears to have no considerable effect on serum glucose and lipid metabolism in streptozotocin-diabetic rats. Therefore, the utility of opium may have no effect on reduction of cardiovascular risk factor in diabetics.

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