

# Effect of Acute Morphine Exposure on Insulin and Blood Sugar Levels in Normal Rats

Alireza Vahidi<sup>1,2</sup>, Mohammad Yahya Vahidi<sup>3</sup>, Mohammad Ebrahim Rezvani<sup>4\*</sup>

1. Department of Pharmacology, School of pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
2. Research and clinical center for infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
3. Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran
4. Department of Physiology, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Received: 10 March 2012 - Accepted: 3 June 2012

## ABSTRACT

**OBJECTIVE:** Social belief and experimental evidences indicate that opium and its alkaloids, morphine, produced hypoglycemic effects in animal models. This study was conducted in order to determine the role of morphine on blood glucose and insulin.

**MATERIAL AND METHODS:** This is an empirical analysis investigating the laboratory albino male rats weighing 200-250 g. Rats in the control group received saline and animals in the treatment group were injected 5mg/kg morphine intraperitoneally (I.P.). Blood glucose and insulin rate were measured at the time of 0, 2, 4 and 6 hours after morphine injection.

**RESULTS:** The results of this study showed that morphine could not change serum insulin and blood glucose in comparison to control group.

**CONCLUSION:** It is concluded that the effects of morphine on blood glucose and insulin are dependent upon the route of administration, and that I.P. injection of morphine in rat had no effect on blood levels of glucose and insulin.

**KEY WORDS:** Morphine, Hyperglycemia, Insulin, Rats.

## INTRODUCTION

There are evidences that indicate morphine, which is used as a supplement for general anesthesia, induces hyperglycemia in conscious rabbits (1, 2) cats (3,4) and dogs (5). These results were confirmed by infusing beta endorphins intracisternally in conscious, unrestrained, adult male rats. This study showed an increase in plasma glucose by the infusion. Also, it could abolish the effect via adrenal denervation. Disabling neural control of the adrenal gland disrupted the production of cortisol, eliminating the stimulus for the development of hyperglycemia (6). Morphine potently stimulates the secretion of both glucagon and insulin; therefore, the direct

action of the opiate is increased on the islet cells of the pancreas. It has been shown that an intravenous dose of morphine (0.5 mg/kg) elevates plasma insulin and glucagon in intact dogs. These hyperglycemic effects can be blocked by naloxone in dogs. In rats, naloxone in low doses (2 mg/kg, i.v.), could not produce any significant effect, but in high doses (10 mg/kg, i.v.) led to hyperglycaemia (8). In addition, in conscious fasted rats, prazosin as an  $\alpha_1$  adrenergic antagonist increased glucose levels and exacerbated the hyperglycaemic effects of UK14304, an  $\alpha_2$  adrenergic agonist, and adrenaline (9). In contrary to widespread hyperglycemic effect of morphine in several species of animals, a hypoglycaemic effect has

\*Correspondence: Mohammad Ebrahim Rezvani, Department of Physiology, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Tel: (+98) 351-8203410. Email: erezvani@yahoo.com

been reported when it administrates intrathecally in normal non-fasted concisions rats (10) and mice (10).

Generally, these evidences indicate that animals reveal different sensitivity to hyperglycemic effects of morphine or naloxone (I.C.V. or I. V. injection) and this sensitivity depends on the site of drug injection, the species used and conditions of animals.

Based on these data, this study was conducted to evaluate effect of morphine (intraperitoneally, I.P.) on serum insulin and glucose level in fasted unanesthetized rats.

## MATERIALS AND METHODS

### Animal

Male wistar rats weighing 180-200 g were housed in the animal house at the shahid sadoughi University of Medical Sciences in 22-23°C temperature and humidity-controlled rooms. The animals were fed with standard dietary pellet. All rats were acclimatized to animal house with a 12-h light-dark cycle for a period of 2 weeks before the experimental manipulation. Principles of laboratory animal care were followed, and experimental protocols were approved by the ethic committee of shahid Sadoughi University of medical sciences.

### Drug Preparations and Injections

Drugs were morphine HCl (Daropakshh, Tehran, Iran), obtained as ampoules of 15 mg/ml and saline (0.9% NaCl solution) was used as the vehicle for morphine. Insulin kit was produced by Merodica Company (Sweden). Glucose kit was purchased from Pars Azmun Company (Tehran, Iran). Morphine HCL was injected I.P.

### Experimental Procedures

Twelve-hour Fasted rats were allocated into four groups: control rats received artificial extracellular fluid (I.P., n = 5), whereas other rats were given morphine 5 mg/kg (n = 5); the blood collections were performed in 0, 2, 4 and 6 hours after morphine injection by retro-orbital sinus puncture. Serum was analyzed for

glucose and insulin. Insulin was determined by radioimmunoassay with ELIZA-2943 kit.

### Statistical Analysis:

Data were analyzed using SPSS 17 for Windows (SPSS Inc., Chicago). Multiple ANOVA was used for comparing alternations of serum insulin and glucose levels between the groups in different times. The post-hoc Tukey's test was performed to compare the groups. In all the analyses,  $P < 0.05$  were considered as statistical significant level.

## RESULTS

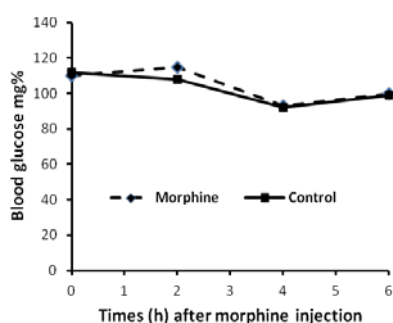
Baseline serum glucose concentration before and 2, 4 and 6 hours after I.P. injection of morphine (dose) were compared. In all the steps, morphine failed to affect serum glucose concentrations significantly. In control and morphine treated groups, a statistically non-significant hypoglycemic effect was obtained at 4 and 6 hours after morphine or saline injection (fig. 1).

Blood insulin concentration was also measured. The rats did not show any significant change in blood insulin concentration at 2, 4 and 6 hours after morphine treatment. Both control and morphine treated rats demonstrated a reduction in the blood glucose and insulin concentration at 4 and 6 hours after treatment (fig. 2).

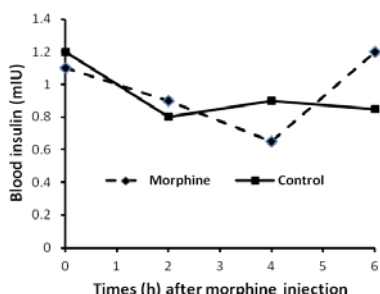
## DISCUSSION

The present study results proposed that the serum insulin and blood glucose did not show significant changes after morphine administration. Morphine administration can induce hyperglycemia or hypoglycemia depending on animal species and rout of injection.

Hyperglycemia after morphine administration was mediated by central nervous system, and induced adrenal excitation and the subsequent changes in liver function (11). Morphine also stimulates the secretion of insulin and glucagon (12). Yohimbine, when injected intravenously, inhibited Hyperglycemia in response to i.v. morphine, whereas naloxone was decreased by the hyperglycemia because



**Figure 1- Effect of Morphine on the Blood Glucose Levels of Fasted Conscious Rats. Control animals received saline (I.P.). There were not significant differences in blood glucose between control and morphine groups**



**Figure 2- Effect of Morphine on the Blood Insulin Levels of Fasted Conscious Rats. There were not significant differences in blood insulin between control and morphine groups**

centrally mediated morphine induced hyperglycemia was prevented by centrally injections of yohimbine; it was suggested that centrally mediated morphine hyperglycemia may be mediated through  $\alpha_2$ -adrenoceptors, whereas the peripherally mediated morphine hyperglycemia is induced via pathways controlled by  $\alpha_2$ -adrenoceptors with opioid mechanisms (13). However, colocalization of opioid receptor and  $\alpha_2$ -adrenoceptors has been observed in many brain sites (14).

A hypoglycemic effect in response to centrally

morphine administration has been reported in non-fasted conscious rats and mice (1-5). It is concluded that the hypoglycemic effect of i.t. morphine appears to be independent of its behavioral effects, displays tolerance, and is accompanied by hepatic glycogen depletion. Morphine-induced hypoglycemia in mice did not mediate via insulin dependent mechanism and it may mediate through a central  $\alpha_2$ -adrenergic pathway (15).

In the present study, we indicated that morphine I.P. failed to induce hyper- or hypoglycemia in conscious fasted rats. Hyperglycemia was mediated by  $\alpha_1$ -adrenoceptors in response to morphine and naloxone. The selective  $\alpha_1$ -adrenoceptor antagonist did not produce any hyperglycemic effect. Furthermore, it did not influence the rise in blood glucose levels in responses to i.c.v. or i.v. naloxone (16-17). These findings indicate that  $\alpha_1$ -Adrenoceptors are not involved in naloxone-induced hyperglycaemia. The  $\alpha_2$ -adrenoceptor antagonist markedly antagonized the hyper-glycaemic actions of adrenaline, whereas it could not produce any change in blood glucose. Stimulation of central  $\alpha_2$ -adrenoceptors induces hyperglycemia which this effect is prevented by prior treatment with  $\alpha_2$ -adrenoceptor antagonist administration (18).

In General, it is concluded that the effects of morphine on blood glucose and insulin are dependent upon the route of administration. Moreover, I.P. injection of morphine in rat had no effect on blood levels of glucose and insulin. Further studies are needed to clarify the relationship between the adrenergic and morphine regarding route of their injections.

## REFERENCE

1. Abouazra HA, Sharif S. Hyperglycaemia: a morphine-like effect produced by naloxone. *Clinical and Experimental Pharmacology and Physiology*. 2001;28(4):300-5.
2. May CN, Whitehead CJ, Dashwood MR, Mathias CJ. Investigation of the central sites at which morphine acts to cause hypertension in conscious rabbits. *British journal of pharmacology*. 1989; 97(3): 873-81.
3. Borison HL, Fishburn BR, Bhide NK, McCarthy LE. Morphine-induced hyperglycaemia in the cat. *Journal of Pharmacology and Experimental Therapeutics*. 1962;138(2): 229-35.
4. Feldberg W, Pyke DA, Stubbs WA. Hyperglycaemia, a morphine-like effect produced by naloxone in the cat. *The Journal of Physiology*. 1983; 340(1): 121-8.

5. Ipp E, Schusdziarra V, Harris V, Unger RH. Morphine-induced hyperglycaemia: Role of insulin and glucagon. *Endocrinology* 1980; 107(2): 461–3.
6. van Loon GH, Appel NM. beta-Endorphin-induced hyperglycemia is mediated by increased central sympathetic outflow to adrenal medulla. *Brain research*. 1981;204(1):236-41.
7. Ipp E, Dobbs R, Unger RH. Morphine and b-endorphin influence the secretion of the endocrine pancreas. *Nature* 1978; 276: 190–5.
8. Pacula P, Janicki PK, Krzascik P. Effects of naloxone on glucose levels in the hepatic venous plasma in the rat. *Clinical and Experimental Pharmacology and Physiology* . 1987; 14(11-12): 911-3.
9. Berridge TL, Doxey JC, Roach AG, Smith CFC. Selectivity profile of the alpha2-adrenoceptor antagonist efaroxan in relation to plasma glucose and insulin levels in the rat. *European journal of pharmacology*. 1992; 213(2): 205–12.
10. Brase DA, Singha AK, Estrada U, Lux F, Dewey WL. Hypoglycemia induced by intrathecal opioids in mice: Stereoselectivity, drug specificity and effect of fasting. *J. Pharmacol. Exp. Ther.* 1990; 253(3): 899–904.
11. Surwit RS, Feinglos MN, Scovern AW. Diabetes and behavior: A paradigm for health psychology. *American Psychologist* 1983;38(3):255-62.
12. Surwit RS, McCubbin JA, Kuhn CM, McGee D, Gerstenfeld D, Feinglos MN. Alprazolam reduces stress hyperglycemia in ob/ob mice. *Psychosomatic medicine* 1986;48(3):278-82.
13. Sharif SI, Gupta KP, Benjalel M. Studies on the mechanism of morphine hyperglycaemia in rabbits. In: The National Health and Drug Center (ed.). *Proceedings of The Second Jamahiriya Conference on Medical Naloxone and hyperglycaemia* 305 Sciences, 6–8 May 1994, Benghazi, Libya. Al-Arab Medical University, Benghazi. 1994; 31–5.
14. Lamah J, Eiger S, Sadee W. Interaction among mu-opioid receptors and [alpha]2-adrenoceptors on SH-SY5Y human neuroblastoma cells. *European Journal of Pharmacology: Molecular Pharmacology*. 1992; 227(1): 19–24
15. Lux F, Han YH, Brase DA, Dewey WL. Studies on the mechanism of hypoglycemia induced by intrathecal morphine: dissociation from behavioral effects, effects of tolerance and depletion of liver glycogen. *Journal of Pharmacology and Experimental Therapeutics*. 1989;249(3):688-93.
16. Nakadate T, Nakaki T, Muraki T, Kato R. Adrenergic regulation of blood glucose levels: Possible involvement of post synaptic  $\alpha_2$  type adrenergic receptors regulating insulin release. *Journal of Pharmacology and Experimental Therapeutics*. 1980; 215(1): 226–30.
17. Nakadate T, Nakaki T, Muraki T, Kato R. Regulation of plasma insulin level by  $\alpha_2$ -adrenergic receptors. *European journal of pharmacology*. 1980; 65(4): 421–6.
18. Garcia-Barrado MJ, Sancho C, Palomero J, Moratons J. Role of alpha2-adrenoceptors on the hyperglycaemic and insulin secretory effects derived from alpha1- and beta-adrenoceptor stimulation in the rabbit. *Journal of autonomic pharmacology*. 1998;18(5):287–95.