

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

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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 α_1 adrenergic antagonist increased glucose levels and exacerbated the hyperglycaemic effects of UK14304, an α_2 adrenergic agonist, and adrenaline (9). In contrary to widespread hyperglycemic effect of morphine in several species of animals, a hypoglycaemic effect has

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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

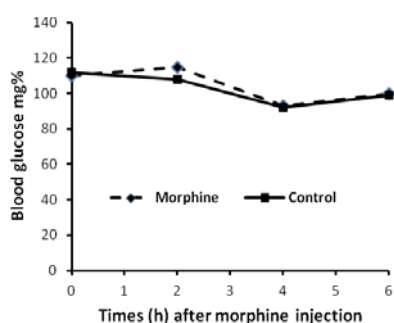


Figure 1- Effect of Morphine on the Blood Glucose Levels of Fasted Conscious Rats. Control animals received saline (I.P.). There were not significant differences in blood glucose between control and morphine groups

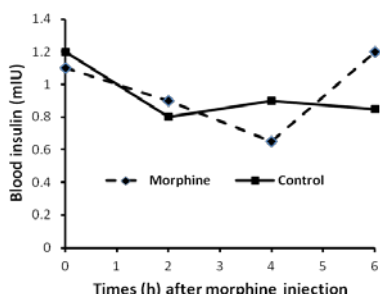


Figure 2- Effect of Morphine on the Blood Insulin Levels of Fasted Conscious Rats. There were not significant differences in blood insulin between control and morphine groups

centrally mediated morphine induced hyperglycemia was prevented by centrally injections of yohimbine; it was suggested that centrally mediated morphine hyperglycemia may be mediated through α_2 -adrenoceptors, whereas the peripherally mediated morphine hyperglycemia is induced via pathways controlled by α_2 -adrenoceptors with opioid mechanisms (13). However, colocalization of opioid receptor and α_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 α_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 α_1 -adrenoceptors in response to morphine and naloxone. The selective α_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 α_1 -Adrenoceptors are not involved in naloxone-induced hyperglycaemia. The α_2 -adrenoceptor antagonist markedly antagonized the hyper-glycaemic actions of adrenaline, whereas it could not produce any change in blood glucose. Stimulation of central α_2 -adrenoceptors induces hyperglycemia which this effect is prevented by prior treatment with α_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.

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