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Effect of hyperglycemia on the efficacy of morphine analgesia in rats.

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Summary

The effect exerted by hyperglycemia on the analgesic potential of morphine was studied in female Wistar rats with the hotplate device and the formalin test. Hyperglycemia induced by an intraperitoneal (ip) injection of alloxan (40mg/Kg) significantly ($p<0.05$) reduced the potency of morphine in the two tests employed. While morphine caused an inhibition of 48.64% (44.83 ± 3.69s vs 30.16 ± 4.12s) in the pain sensitivity of control non-diabetic animals using the hotplate device, an inhibition of only 36.25% (31.50 ± 2.28s Vs 23.12 ± 1.80s) was recorded in the pain sensitivity of the diabetic group using the same method. In the formalin test, morphine inhibited the pain sensitivity by 35.23% (1.93 ± 0.17 Vs 1.25 ± 0.21) in the control non diabetic group and by 25.93% (2.16 ± 0.09 Vs 160 ± 0.15) in the diabetic group. From these data, it is hypothesized that the hyperglycemic state is responsible for selectively affecting the potency of morphine. These results , if found to be true in man , may have clinical implications for the use of morphine in diabetic subjects

Keywords: *Analgesia ,morphine and hyperglycemia*

Résumé

Cette revue rétrospective avait pour but de déterminer le taux de l'impact de l'extraction du 3iéme molaire et la souffrance associée aux patients de moins ou égale a 40 ans ayant besoin d une chirurgie pour l'extraction du 3iéme molaire entre Avril 2001 à Mars 2006 au centre hospitalier universitaire de Lagos, Nigeria. Les données extraites des fichiers de ces patients inclues : l'age, sexe, dent extraite, type d'impaction, souffrance chirurgicale. Au total 6.3% des patients avait besoin d'une extraction chirurgicale du 3ieme molaire. Aucun des patients n'avaient des complications intraoperatives. Seulement 3 patients (9.7%) développaient des complications mineurs de courte durées qui étaient réversible. Moins de 7% des patients ayant besoin d'extraction chirurgicale du 3iéme molaire avaient plus de 40 ans. Ces résultats ne supportent pas l'extraction prophylactique chirurgicale du 3ieme molaire basée sur l'assumption que la souffrance chirurgicale acrroit avec l'age

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Introduction

There are reports in the literature concerning the effects of diabetes in altering the sensitivity of laboratory animals to pharmacological agents. Some reports have demonstrated increased sensitivity of hyperglycemic or diabetic animals to barbiturates [1,2,3.] and decreased sensitivity to d-amphetamine [4.]. David *et al* [6] reported that insulin-induced hypoglycemia potentiated the antinociceptive action of morphine in the rat tail flick test, but failed to report dose-related effects of glucose on morphine potency.

Only a few authors have looked into the association between hyperglycemia and the antinociceptive potential of morphine with conflicting results [7,8.9]. In this study we further investigate this relationship so as to resolve certain aspects of this conflicting evidence.

Materials and methods

Female rats were used since the pathophysiological characteristics of diabetes are reported to be more severe in females than in males [10]. The adult female Wistar rats (180-220g) used were purchased from the pre-clinical animal house of the College of Medicine, University of Ibadan, Nigeria. They were housed in groups of six at room temperature; standard food pellets and water were supplied *ad libitum*.

The animals were divided into two main groups: control and diabetic groups. Each main group was subdivided into two groups I and II and treated as follows:

Control group I - normal saline 10mls/kg i.p
" II - morphine 10mg/kg subcutaneously (sc)

Diabetic group I - normal saline 10mls/kg i.p
" II – morphine 10mg/kg sc

Pain rating was carried out on each of these groups fifteen minutes after the administration of either normal saline or morphine. Each group consisted of six rats.

Induction of diabetes

Following a 48 hour fast, 8 rats received intraperitoneal (i.p) injection of alloxan (40mg/kg). Within 48 hours after alloxan administration, blood glucose concentrations were measured via tail clip sampling. Briefly the tip of the tail (approximately 2mm) was clipped off using a sterile blade and 1-2 drops of blood from the cut surface were used for measurement of blood glucose concentration using the glucose oxidase method. Animals with blood glucose concentrations greater than 250mg/dl were considered diabetic and were the ones selected for the pain rating. [7]

Test for pain thresholds

1. The hot plate test.
   The hot plate latency was measured using the original method of Eddy and Leimbach [11] as modified by Ibironke *et al* [12]. The hotplate temperature was maintained at 55 ± 2 °C and a cut off point of 60s was imposed as repeated application of heat beyond this result in significant tissue damage.
   Pain sensitivity was evaluated by the response latency for paw licking on the hot plate. Latency was measured twice at 15 minutes intervals and the average of the results calculated and recorded
2. The formalin test
   The rats were acclimatized to the experimental arena for 15 minutes and anaesthetized with 5% halothane [13]. Formalin (50μL, 0.25-5%) was injected subcutaneously (sc) into the large lateral foot pad on the plantar surface of the left hind paw. The rats were placed in a transparent rectangular plastic box with the top opened for an unobstructed view of the response to formalin injection which was scored using the weighted scores method [14]. The pain rating was carried out on all the rats in the normal and diabetic groups.

Results

The results of the effect of hyperglycemia on the efficacy of morphine analgesia are as shown in tables 1, 2 and 3. Table 1 showed an increase in hot plate latency and a decrease in formalin score in the control rats. These observations denote an increase in pain threshold and confirm the activity of morphine in decreasing pain sensitivity.

Table 1: Effect of morphine on pain threshold in control rats

Groups	Hotplate Latency(s)	% inhibition of pain sensitivity	Formalin score	% inhibition of pain sensitivity
Control Group I (normal saline)	30.16 ± 4.21	-	1.93 ± 0.17	
Group II (morphine 10mg/Kg)	44.83± 3.69*	48.64	1.25 ± 0.21*	35.23

• *P<0.05 (cf control, n=6).*
Values are means ± standard error of the mean

Table 2 followed the same pattern for the diabetic rats i.e. morphine treatment resulted in an increase in pain threshold of diabetic rats.

Table 2: Effect of morphine on pain threshold in diabetic rats

Groups	Hotplate Latency(s)	% inhibition of pain sensitivity	Formalin score	% inhibition of pain sensitivity
Diabetic Group I (normal saline)	23.12 ± 1.80	-	2.16 ± 0.09	
Group II (morphine 10mg/Kg)	31.50± 2.82*	36.25	1.60 ± 0.15*	25.93

• *P<0.05 (cf control, n=6).*
Values are means ± standard error of the mean

Table 3, extracted from tables 1 and 2 showed that the efficacy of morphine as an analgesic as measured by percentage inhibition had fallen in the diabetic compared with the control animals.

Table 3: Effect of hyperglycemia on morphine antinociception.

Group	Percentage inhibition of pain sensitivity by morphine: Hot plate test	Formalin test
Control	48.64	35.23
Diabetic	36.25	25.93

Discussion

Our results showed that an acute state of hyperglycemia induced by intraperitoneal injection of alloxan can affect the antinociceptive potency of morphine. The results of a number of experiments suggest the hypothesis that the hyperglycemic state is responsible for the observed decrease in the antinociceptive potency of morphine [4]. The exact mechanism of this action is not known, but there have been several submissions by various authors. For example, an experimental model of a glucose-saccharin cocktail, which is thought to enhance the release of endogenous opioid peptides (EOPs) is known to diminish the responsiveness of male Sabra rats to morphine [9,14]. The cocktail was found to oppose the analgesic effects of morphine probably due to the enhancement of EOP secretion. A similar mechanism could explain the resistance to morphine in diabetes because diabetes enhances the

release of EOPs which block the ensuing analgesic effects of morphine.

Further explanation was also provided by Simon *et al*, who suggested that the antagonistic effect exerted by glucose on the opiate receptor could significantly diminish the antinociceptive potency of morphine [15]. This effect could be the consequence of a decrease in receptor number or an alteration in the conformation of the opiate receptor.

We have no facilities in our laboratory to assay opioid receptors or estimate EOP levels, however, we believe that the observations made by these various authors could provide adequate explanation for the decreased antinociceptive potency of morphine observed in our study since their experiments were also based on the hyperglycemic state either in form of glucose-saccharin cocktail or by direct injection of alloxan or streptozotocin.

It should be noted however, that species differences in basal and intermediary metabolism and differences between human diabetes mellitus and the animal models used in these experiments make it difficult to directly assume that human diabetics are less sensitive to the analgesic effects of morphine.

No such reports are available in the literature, perhaps due to the rigid control of serum glucose levels carried out by physicians during hospitalization particularly when surgery is contemplated [16]

In summary, we conclude that alloxan induced diabetes can selectively affect the potency of morphine in rats and the diabetic state that is responsible for the altered potency is the presence of hyperglycemia

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