The Analgesic Effect of Morphine on Postoperative Pain in Diabetic Patients

Karcı A, Tasdogen A, Erkin E, Aktaş G, Elar A

Dept. Of Anesthesiology and Reanimation

Dokuz Eylül University Medical School, İzmir TURKEY

INTRODUCTION

- There is a reduced potency of morphine-induced antinociception in chemically
- On the other hand, hypoglycemia induced by insulin treatment significantly increased morphine potency in the tail-flick test in animals
- There is also considerable evidence that the antinociceptive potency of morphine has decreased in spontaneous diabetic mice

INTRODUCTION

- Hypersensitivity to pain and attenuation of responsiveness to morphine have also been reported in diabetic patients
- BUT; previous discussions of this issue have focused almost exclusively on the relatively poor response of patients with neuropathic pain

AIM:

- To evaluate the effect of hyperglycemia on postoperative acute pain perception
- To compare the analgesic efficacy and the occurrence of side-effects following administration of morphine after abdominal hysterectomy.

MATERIAL & METHOD

- Approval from the institutional Ethics Committee
- (Group D) : 33 NIDDM
- (Group ND) : 31 non-diabetic patients
- ASA physical status I—II
- Aged 24—68 years
- Scheduled for elective TAH ± BSO
- Group D patients received OAD; none of them received insulin for management of diabetes

MATERIAL & METHOD

Exclusion criteria:

- Patients with Type I / II diabetes
- Having signs of neuropathic pain
- Taking medication for neuropathic pain
- Receiving insulin for perioperative glycemic control
- Patients with poor glycemic control
- Patients allergic to morphine or currently receiving opioids for treatment of chronic pain

MATERIAL & METHOD

- Patients who were considered likely to
- remain on postop. PCA for 48 h were selected from the operating lists

- Induction of GA : Fentanyl 2πg.kg^{-1}, and Thiopental (up to 5mg.kg^{-1}) and Vecuronium 0.1mg.kg^{-1}.
- Anesthesia maintenance : Sevoflurane in Oxygen/N_2O (30%/70%)
- A loading dose of morphine(50πg.kg^{-1}) was given during closure of fascia
- Neuromuscular blockade was reversed

MATERIAL & METHOD

- The PCA pump (*Abbott Life Care PCA Plus Infuser-Abbott Laboratories, North Chicago, IL*) was set to deliver :
- Morphine 1mg as a bolus dose / 10 min
- 20mg / 4-h limit with no background infusion
- A member of the Acute Pain Service visited the patients two times a day
- In cases of inadequate analgesia 1mg of M was given as a rescue analgesic
- The main efficacy measurement : accumulated M
- consumption was recorded at emergence and at postop 1, 2, 4, 8, 12, 24 and 48 h

MATERIAL & METHOD

- Pain intensities were assessed using a VRS
- Hemodynamic variables, need for rescue analgesic and occurrence of adverse effects were noted
  t-test, repeated measures ANOVA with Bonferroni correction, Chi-square and Fisher's exact tests were used statistical analyses
- Avalue of $P<0.05$ was considered statistically significant for all analyses.

RESULTS

- There was an increase in blood glucose levels in the
- postop period in both groups [Signif. at the 1. 6th h]
- Mean blood glucose levels in Group D > Group ND in all time periods [statistically significant (P=0.0001).
- SBP & HR in Group D > Non-diabetic group [NS]
- Diabetics made more demands from the PCA
- (141.60±130.27 vs. 79.77±63.97, respectively).
- Difference was significant at the 24th (P=0.046)
- and 48th (P=0.024) hrs
- Correspondingly, diabetic patients received more deliveries from the PCA (Group D: 48.43±24.18; Group ND: 38.97±20.95) [NS]

RESULTS

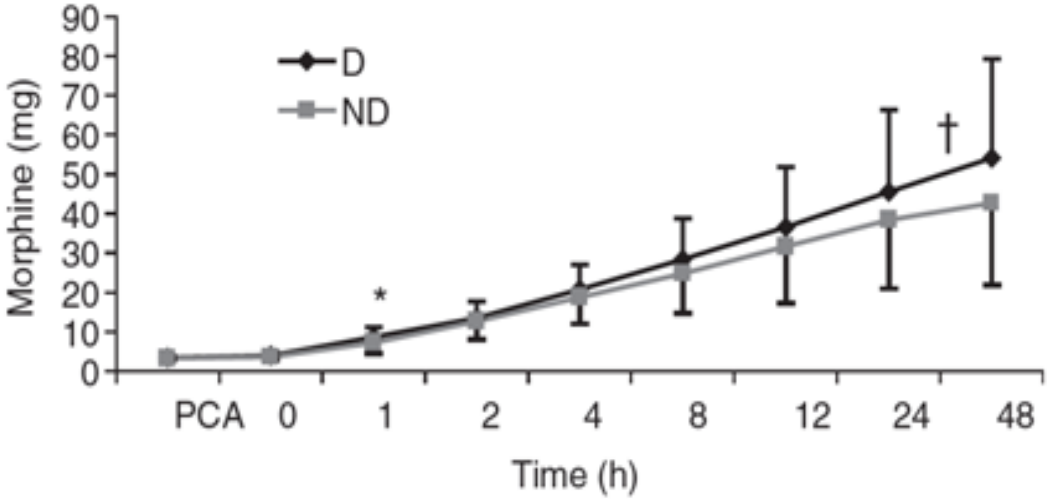
- The cumulative M consumption from PCA

  Diabetic > Non-diabetic

  54.12±25.09mg 42.66±20.67mg

- Difference was statistically higher in the 1st postop
- hour (P=0.037).
- Diabetic patients required more morphine in the last 24 h (P=0.015)
- Cumulative M consumption revealed a linear increase in Group D (P<0.0001), but not in Group ND after 24 h (P<0.001)

RESULTS

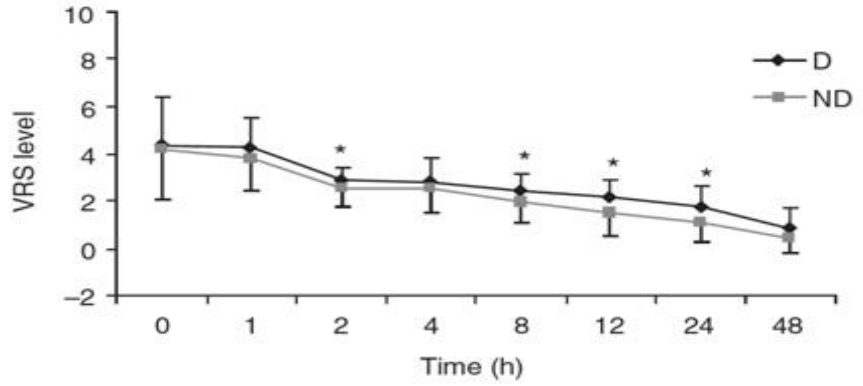


*Opioid consumption of the diabetic and non-diabetic patients in the postoperative period. Data are presented as mean ± SD. *P = 0.037 (cumulative morphine consumption) and †P = 0.015 (morphine consumption in each study period).*

- More patients in the diabetic group required rescue medication (26 vs 19)
- Rescue M doses in diabetic and non-diabetic groups were 2.23±1.99 and 1.63±1.79

RESULTS

- Diabetic patients had higher pain scores at 2, 8, 12 and 24 h (P<0.05)



*Postoperative pain scores of diabetic and non-diabetic patients at rest (mean ± SD). *P < 0.05.*

Pain scores in the study period were significantly higher in diabetic patients compared with non-diabetics (P=0.016)

The decrease in VRS levels in nondiabetic patients was higher than in the diabetic patients (Group ND, P=0.0001; Group D,P=0.001).

- Significantly

RESULTS

- Nausea : Diabetic group / Non-diabetic (25 and 14, respectively; P=0.003)
- Vomiting (8/30; 26.6%) in both groups
- Adverse effects such as shivering,
- drowsiness and constipation were not different

DISCUSSION

The results of this study demonstrated that diabetic patients had hi[WHY?]nd the requirement for morphine w[WHY?]eed for rescue analgesics were [WHY?] postoperative period compared with non-diabetic patients

- Hypersensitivity to pain
- Attenuation of response to morphine in diabetics

DISCUSSION

- The issue of analgesic response to opioids has been evaluated mostly in diabetic neuropathic pain in which pain generation is different from normal homeostatic physiological mechanisms
- And increased doses of morphine are suggested in these reports

- Since properties of pain or pain syndrome appear to be an important determinant of opioid response, all patients were questioned and examined for signs of neuropathy

DISCUSSION

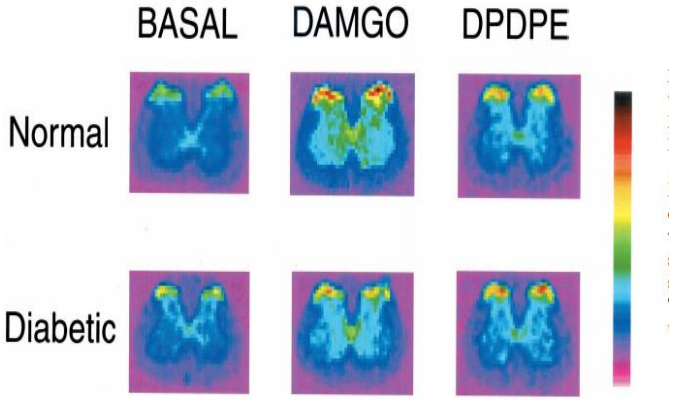
- It is postulated that either hyperglycemia or pharmacokinetic/ pharmacodynamic changes could be responsible for the difference in responsiveness to morphine
- In a model of chronic pain Raz et al. showed a reduction of morphine analgesia in hyperglycemic rats and proposed that hyperglycemia might diminish the analgesic effect of morphine by :
  - A direct antagonistic effect on the opioid Rs
  - A decrease in receptor number
  - An alteration in the conformation of the opiate R
  - A postreceptor effect

Anesthesiology 2002; 97:1602–8

Functional μ Opioid Receptors Are Reduced in the Spinal Cord Dorsal Horn of Diabetic Rats

Shao-Rui Chen, M.D., Kristi L. Sweigart, B.S.,† Joan M. Lakoski, Ph.D.,‡ Hui-Lin Pan, M.D., Ph.D.§*

- Functional μ opioid receptors in the spinal cord dorsal horn of diabetic rats are reduced
- Impaired functional receptors constitute one of the mechanisms underlying the reduced spinal analgesic effect of μ opioids in diabetic neuropathic pain



DISCUSSION

Pharmacology letter Accelerated communication

Modulation by serum glucose levels on morphine-induced antinociceptive effect in C57BL/KsJ-db/db mice

Junzo Kamei[a], Midori Sodeyama[a], Masahiro Ohsawa[a], Mari Kimura[a], Shun-ichi Tanaka[a]

- antinociceptive effect of morphine between CS-045-treated C57BL/KsJ-db/db mice and C57BL/KsJ-db/++ mice. Adoptive transfer of supernatant of the spleen cell homogenate from C57BL/KsJ-db/db mice to naive ICR mice had no significant effect on the recipients' antinociceptive sensitivities to s.c. morphine. These findings support the our previous suggestion that some factor(s) derived from spleen mononuclear cells is the prime factor involving the insulin-insensitive mechanisms for the reduction of μ-opioid agonist-induced antinociception during the severe stages of diabetes.

Role of L-type Ca^{2+} channels in attenuated morphine antinociception in streptozotocin-diabetic rats

Srinivas Gullapalli, Krishnamoorthy Gurumoorthy, Chaman Lal Kaul, Poduri Ramarao

- Nimodipine (0.1–3 mg/kg, i.p.) did not produce antinociception but significantly potentiated the morphine response in control rats. Nimodipine (0.3–3 mg/kg, i.p.) reversed the attenuation of morphine antinociception in a dose-dependent manner in diabetic rats. Moreover, insulin (2 μ/kg, s.c.) reversed the attenuated morphine antinociception in streptozotocin-diabetic rats. A significant increase in the B_{max}

DISCUSSION

- Moreover Oyibo et al. and Fox et al. have reported that stable glycemic control and maintenance of euglycemia were important in the management of pai in diabetic neuropathy

- THUS; these findings show a direct relationship between blood glucose levels and morphine sensitivity

DISCUSSION

PHARMACOKINETICS

- Total clearance
- Vol of distribution of morphine are increased in diabetic rats

Diabetes-induced glycosylation of proteins which can alter the protein binding and increase the unbound fraction of morphine

Courteix C, J Pharmacol Exp Ther 1998

Gwilt PR, Clin Pharmacokinet 1991

DISCUSSION

Is the Reduced Efficacy of Morphine in Diabetic Rats Caused by Alterations of Opiate Receptors or of Morphine Pharmacokinetics?

C. COURTEIX, P. BOURGET,[1] F. CAUSSADE,[2] M. BARDIN,[3] F. COUDORE, J. FIALIP and A. ESCHALIER[3]
Equipe NPPUA, Laboratoire de Pharmacologie, Faculté de Pharmacie, F-63001 Clermont-Ferrand Cedex, France
Accepted for publication December 12, 1997 This paper is available online at: http://www.jpet.org

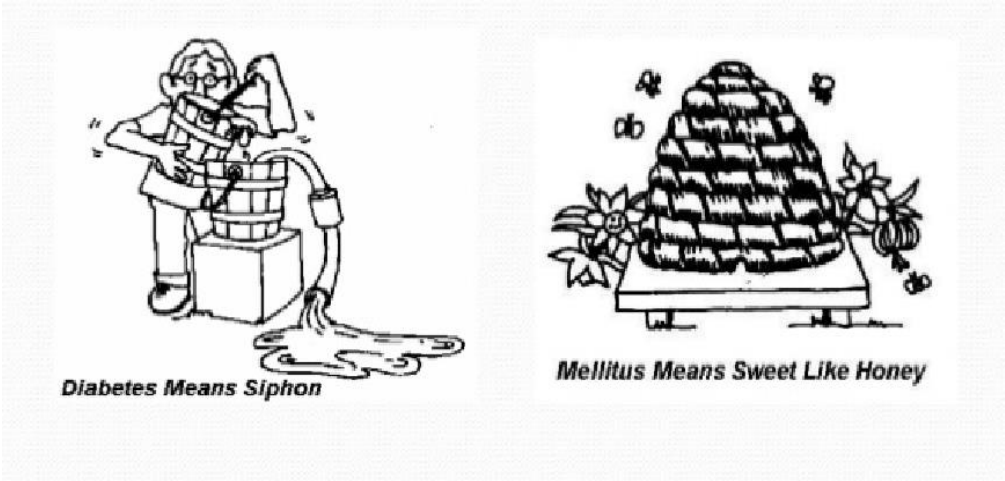
ABSTRACT

Because it generally is admitted that neuropathic pain is resistant to opioid analgesia, we investigated the effect of morphine on hyperalgesia in streptozocin-induced diabetes in rats. The antinociceptive effect of morphine (0.5–4 mg/kg i.v.) on mechanical (paw pressure test), thermal (tail immersion test) and chemical (formalin test) hyperalgesia was reduced. To clarify the mechanisms involved in the alteration of morphine analgesia, the binding characteristics of *mu* and *delta* receptor agonists and the pharmacokinetics of morphine and its glucuronide metabolites morphine 3-glucuronide and morphine 6-glucuronide were determined. K_D and B_{max} values for [^{3}H][D-Ala^2,(Me)Phe^4, Gly(ol)^5]enkephalin and [^{3}H][D-Pen^2,D-Pen^5]enkephalin to cerebral *mu* and *delta* opiate receptors were not altered by diabetes. Likewise, the plasma maximal concentration of morphine and metabolites, as well as the area under the curve, did not differ between diabetic and normal rats. Only the total clearance and the apparent volume of distribution of morphine were increased in diabetic rats, which suggests that the diabetes-induced glycosylation of proteins might increase the distribution of morphine in the aqueous compartment. These data indicate that the reduced analgesic effect of morphine caused by diabetes cannot be explained by a decrease in opiate-receptor affinity or density but rather by kinetic alteration of morphine (increase of total clearance and of volume of distribution in comparison with healthy animals).

- Diabetes might alter morphine requirements for postoperativ pain treatment
- Reasons :
  - Diabetes-related changes in morphine P / P
  - Direct effects of hyperglycemia.
  - Hypersensitivity to pain in diabetics should be remembered as a reason for the increased morphine requirement

Diabetes Mellitus

- "Diabetes" comes from the Greek word for "siphon", and implies that a lot of urine is made
- The second term, "mellitus" comes from the Latin word, "mel" which means "honey", and was used because the urine was sweet




2030 First 10 countries (mil)
USA
30,3
Brazil
11,3
Egypt
6,7
2000; 2,920,000
2030: 6,422,000
Pakistan
13,9
India
79.4
China
42,3
Japan
8,9
Indonesia
21,3
Filipinnes
7,8

- 12-25% DM /hospitalized adult patients
- More diabetic patients are operated (25%
- Periop complications associated with DM are increasing
- Related to the end-organ damage

  Mortality Rates X 5 !!!
- Chronic complications resulting in retinopathy, nephropathy, neuropathy and atherosclerosis increase the need for surgical intervention

J Pharmacol Exp Ther. 1981 Aug;218(2):324-9.

Narcotics and diabetes. II. Streptozotocin-induced diabetes selectively alters the potency of certain narcotic analgesics. Mechanism of diabetes: morphine interaction.

Simon GS, Borzelleca J, Dewey WL.

- STZ-induced diabetic rats (IDDM) and genetically diabetic (NIDDM) are significantly less responsive to the antinociceptive effect of M in the tail-flick test
- They postulated; hyperglycemia might interfere with morphine action on the opioid receptor
- The interaction between STZ-induced diabetes and morphine antinociception does not appear to be due to differences in : absorption, distribution or elimination of morphine between diabetic and nondiabetic mice

ELSEVIER

Volume 62, Issue 1, 28 November 1997, Pages PL1–PL6

Pharmacology letter Accelerated communication

Modulation by serum glucose levels on morphine-induced antinociceptive effect in C57BL/KsJ-db/db mice

Junzo Kamei[a], Midori Sodeyama[a], Masahiro Ohsawa[a], Mari Kimura[*], Shun-ichi Tanaka[*]

Japan. J. Pharmacol. 60, 133 – 140 (1992)

Effects of Morphine on Responses of Nociceptive Ventrobasal Thalamic Neurons in Diabetic Rats

Junzo Kamei, Taro Aoki, Hideki Hitosugi, Yuriko Iwamoto and Yutaka Kasuya

- The antinociceptive effect of [DAla 2,MePhe4,Gly-ol5]enkephalin (DAMGO), is decreased in STZ-diabetic mice

Eur J Pharmacol. 1983 Jun 17;90(4):437-9.

Modification of morphine antinociceptive response by blood glucose status: possible involvement of cellular energetics.

Singh IS, Chatterjee TK, Ghosh JJ.

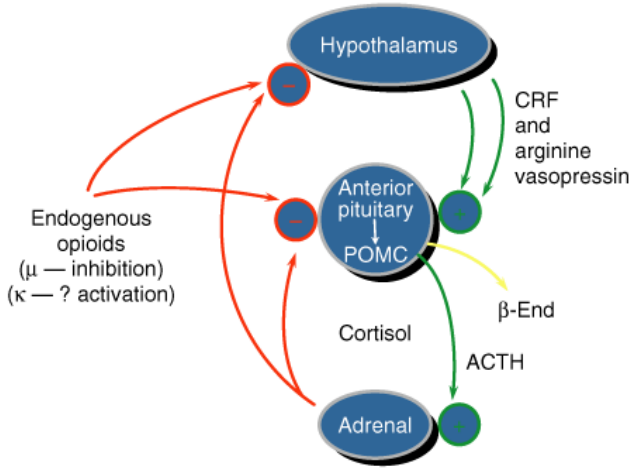
- The antinociceptive response to morphine was enhanced in insulin-hypoglycemic animals

Arch Int Pharmacodyn Ther. 1992 Jul-Aug;318:13-20.

Morphine analgesia in normal and alloxanized mice.

Ginawi OT

- Multiple injections of insulin replacement abolished the decrease in morphine analgesia in diabetic mice



- Hyperglycemia in diabetes alters hypothalamic-pituitary function
- Effects the activity of endogenous opiate system
- Changes in the concent. brain / blood glucose levels modulate opioid antinociception and basal nociceptive processes
- DM is a chronic stress state and the decreased level of β-endorphin in diabetics may induce changes in opiate receptor activity within the brain
- Tolerance develops to exogenous opiates
- THUS, diabetic animals would be more tolerant to the analgesic effects of exogenous opiates

ELSEVIER

ScienceDirect

European Journal of Pharmacology 584 (2008) 78–86

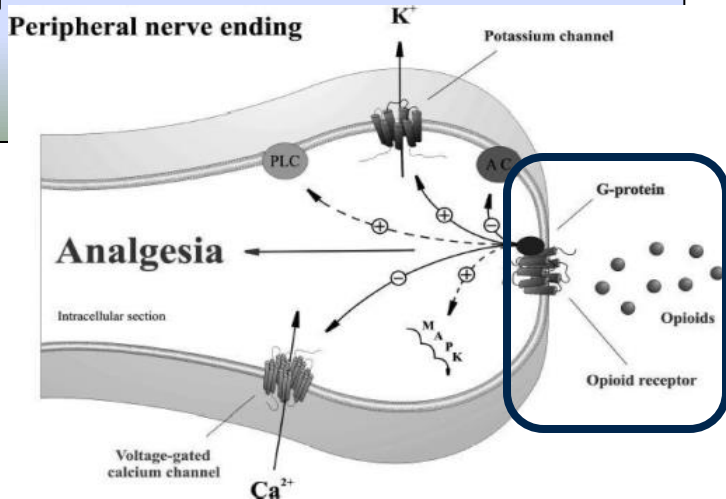
ejp

www.elsevier.com/locate/ejphar

Decreased basal endogenous opioid levels in diabetic rodents: Effects on morphine and delta-9-tetrahydrocannabinoid-induced antinociception

Jovan Williams, Victoria L. Haller *, David L. Stevens, Sandra P. Welch

- Diabetes itself may play a role in modulating the ability of morphine to release endogenous opioids
- Impairment of μ opioid R /G-protein coupling
- G-protein activation by μ opioid receptor agonists is reduced in the spinal cord dorsal horn in diabetic animals



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European Journal of Pharmacology 435 (2002) 187–194

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Role of L-type Ca^{2+} channels in attenuated morphine antinociception in streptozotocin-diabetic rats

Srinivas Gullapalli, Krishnamoorthy Gurumoorthy, Chaman Lal Kaul, Poduri Ramarao *

- Ca^{2+} alters intracellular events to antagonize the antinociceptive effects of morphine
- Ca^{2+} channel blockers, potentiate m-opioid receptor agonist-induced antinociception
- Complications associated with chronic DM such as hypertension, macro/microvascular disease, cataracts, cardiomyopathy, neuropathy etc., may be related to the pronounced changes in
- cellular Ca^{2+} homeostasis .

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European Journal of Pharmacology 570 (2007) 66–71

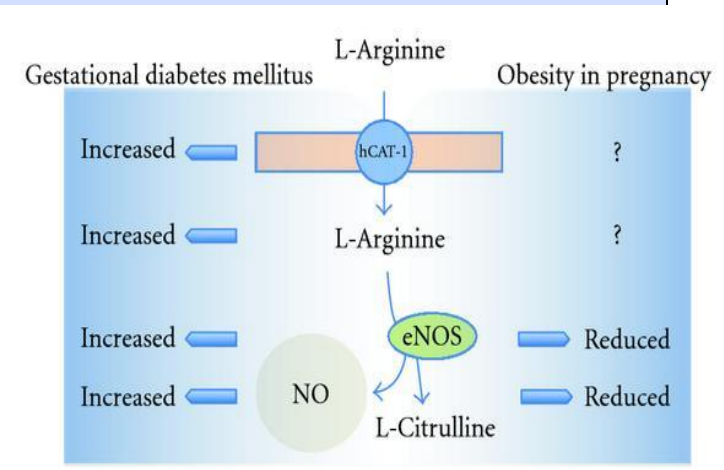
ejp

www.elsevier.com/locate/ejphar

The role of nitric oxide in diabetes-induced changes of morphine tolerance in rats

Khojasteh Joharchi, Masoumeh Jorjani *

- The role of NO as a major neurotransmitter in morphine antinociception and tolerance has been established
- L-arginine, reduces the antinociceptive effect of morphine
- cNOS inhibitors potentiate morphine analgesia in the tail-flick test



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The role of nitric oxide in diabetes-induced changes of morphine tolerance in rats

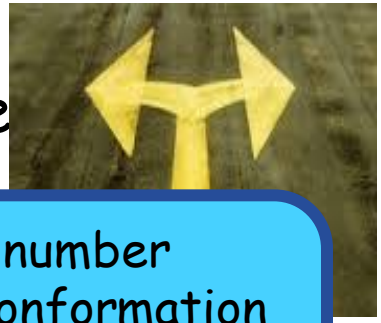
Khojasteh Joharchi, Masoumeh Jorjani *

- It is suggested that the increased urinary nitrite content in morphine tolerated rats may be due to the increased NO production
- There is the same possibility in diabetic state
- Decrease in morphine antinociception in morphine tolerated diabetic rats could be explained by increase of NO production

consequence of a decrease
in receptor number, an alteration in the conformation of the opiate receptor, or a postreceptor effect.

- Raz J et al propose that pain threshold is maintained

Antagonistic effect of glucose



Compensatory increase secretion of endogenous opioid peptides

Decrease in receptor number
An alteration in the conformation of the opiate receptor
Postreceptor effect

In Chronic Painful Diabetic Neuropathy, these normal analgesic response mechanisms may be overwhelmed :

- An excess of nociceptive impulses from diseased peripheral nerves
- Failure of endogenous opioid secretory response to hyperglycemia

Raz I, Hasdai D Diabetes 1988; 37: 1253–9.

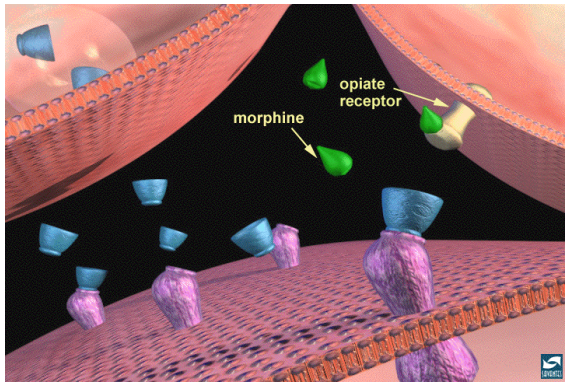
Pain
Volume 57, Issue 2, May 1994, Pages 153–160

Research report

Study of the sensitivity of the diabetes-induced pain model in rats to a range of analgesics

C. Courteix, M. Bardin, C. Chantelauze, J. Lavarenne, A. Eschalier

- Doubled the morphine doses to obtain the same score variation
- Proposed that changes in m-opioid receptors (a pharmacodynamic effect) may be involved in the reduced sensitivity of diabetic animals to M
- Effect of diabetes at the opioid-receptor site; direct effects of hyperglycemia and pharmacodynamic changes of IDDM



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ISSN 0022-3573

Research Paper

The pharmacokinetics of morphine and its glucuronide conjugate in a rat model of streptozotocin-induced diabetes and the expression of MRP2, MRP3 and UGT2B1 in the liver

Yoshitaka Hasegawa[a,b], Shuichi Kishimoto[a,b], Naoki Shibatani[a],

- The weak analgesic effect of morphine in diabetes is controlled by a complex mechanism
- Plasma morphine concent.

  STZ diabetic group < Controls
- Albumin levels were comparable
- The elimination processes, elimination halflife were similar in the two groups

Increased volume of distribution

Where are we in the Clinic ??

Pain. 1990 Dec;43(3):273-86.

The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions.

Portenoy RK[1], Foley KM, Inturrisi CE.

Author information

Abstract

In recent years, the observation that the response of patients to opioid drugs may be influenced by properties inherent in the pain or pain syndrome, such as its pathophysiology, has evolved into the belief that certain types of pain, e.g., neuropathic pains, may be unresponsive to these drugs. This concept has important implications for both clinical practice and basic understanding of opioid mechanisms. We critically evaluate opioid

hydromorphone. From this analysis, we hypothesize that (1) opioid responsiveness in man can be defined by the degree of analgesia achieved during dose escalation to either intolerable side effects or the occurrence of 'complete' or 'adequate' analgesia; (2) opioid responsiveness is a continuum, rather than a quantal phenomenon; (3) opioid responsiveness is determined by a diverse group of patient characteristics and pain-related factors, as well as drug-selective effects; and (4) a neuropathic mechanism may reduce opioid responsiveness, but does not result in an inherent resistance to these drugs. Given the complexity of factors contributing to opioid responsiveness and the observation that outcome cannot be reliably

monitoring of analgesia and other effects.

- Hypersensitivity to pain
- Limited analgesic effect of M in treatment of painful diabetic neuropathy
- Attenuation of responsiveness to morphine

glucose-loaded normal subjects

Where are we in the Clinic ??

- 50 g glucose infusion in normal subjects
- Significant decrease in threshold level of pain
- Significant decrease in maximal level of pain tolerated
- It is concluded that elevated glucose levels and/or rapid fluxes in glucose levels result in a decrease in pain tolerance

.

Where are we in the Clinic ??

- These findings have potential clinical implications in the pathophysiology and management of painful diabetic neuropathy and the use of narcotic agents in diabetes mellitus
- Properties of pain or pain syndrome appear to be an important determinant of opioid response

Limitations of Our Study

- The patients Type II and NIDD
- None of them received insulin for blood glucose control
- They did not have a neuropathic pain
- Individuals with IDD have a longer history of diabetes
- Perioperative approach for blood sugar control in IDD differs from NIDD
- The diabetic group were either normoglycemic or had a mild elevation in blood glucose levels

What Is Found In the Clinic ??

DM

The relationship between blood glucose excursions and painful diabetic peripheral neuropathy: a pilot study

S. O. Oyibo, Y. D. M. Prasad, N. J. Jackson, E. B. Jude and A. J. M. Boulton

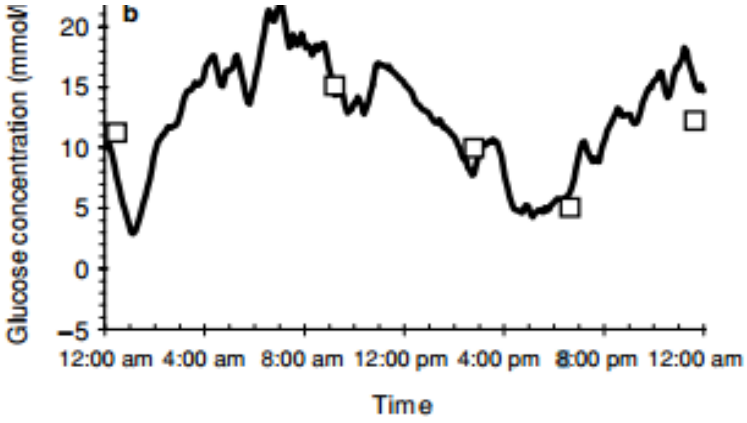

Figure 1 (a) A 24-h continuous glucose monitoring system (CGMS) profile for a patient with painless neuropathy. (b) A 24-h CGMS profile for a patient with painful neuropathy. □, Meter value; —, sensor value.

glycaemic excursions are extreme.

In conclusion, diabetic patients with painful neuropathy seem to have increased blood glucose flux and perhaps poorer glycaemic control compared with those with painless neuropathy. Larger studies are needed to confirm these preliminary observations. If painful symptoms are related to blood glucose excursions, then improved blood glucose stability may benefit patients with painful diabetic neuropathy.

Acknowledgements

This work was financially supported by the Peter Kershaw Trust Fund.

- There is a direct relationship between blood glucose
- levels and morphine sensitivity.
- Total clearance incresed
- Volume of distribution of morphine increased in diabetic rats

Diabetes-induced glycosylation of proteins

(Reported previously in diabetic patients)

- Alters protein binding and increase the unbound fraction of morphine

High diffusion of morphine in the aqueous compartment,

Decrease of its amount in the target organs (CNS)

Reduced effect and larger consumption of morphine in diabetic patients

- In diabetics, hypersensitivity to pain and attenuation of responsiveness to morphine are reported
- Effects the activity of endogenous opiate system
- Changes in the concent. brain / blood glucose levels modulate opioid antinociception and basal nociceptive processes

*Take home message