Effect of Hyperglycemia on Pain Perception and on Efficacy of Morphine Analgesia in Rats

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The effect exerted by different hyperglycemic states on the pain threshold and on the analgesic potential of morphine was studied in male Sabra rats with the hot plate device. Hyperglycemia induced by an intraperitoneal injection of 0.014 mol/kg glucose or an acute or chronic diabetic state induced by streptozocin injection did not significantly alter the pain threshold. However, states of acute and chronic diabetes markedly blunted the analgesic effect of morphine (5 mg/kg). Sabra rats maintained on a cocktail of glucose-saccharin, thought to activate the release of endogenous opioids, demonstrated an increased pain threshold and rapidly developed resistance to the analgesic effect of morphine. Previous studies have shown that glucose in high concentration may interfere with the interaction of morphine on the opiate receptor. The influence of the diabetic state on β-endorphin synthesis and concentration in the central nervous system is another factor that might change pain perception in diabetes. We propose that in diabetes, generally, the pain threshold is adequately maintained, despite the antagonistic effect of glucose, partly due to a compensatory increased secretion of endogenous opioid peptides. We hypothesize that in patients with chronic painful diabetic neuropathy, these normal analgesic response mechanisms may be overwhelmed either by an excess of nociceptive impulses from diseased peripheral nerves or conceivably by a failure of endogenous opioid secretory response to the hyperglycemia. *Diabetes* 37:1253–59, 1988

Pain is a common manifestation of diabetic neuropathy (1); however, the etiology of the neuropathic pain is still not determined. Diabetic neuropathic pain may originate from regenerating axon sprouts (2,3). However, diabetic subjects with such neural changes may not experience neuropathic pain (4). Metabolic factors may also contribute to the development or amelioration of diabetic neuropathic pain (5,6); stringent regulation of blood glucose levels in diabetic subjects resulted in the amelioration of the painful symptoms (5). Thus, painful diabetic neuropathy may be the result of an interplay between peripheral neuropathy and the metabolic changes in the central nervous system caused by the diabetic state.

Simon and associates (7,8) demonstrated a decrease in sensitivity to morphine in streptozocin-induced diabetic (STZ-D) rats. They postulated that glucose might interfere with morphine action on the opiate receptor. Shook and Dewey (9) reported a diminished development of physical dependence on morphine in diabetic animals. They also demonstrated that high glucose concentrations in vitro have decreased the potency of normorphine in the electrically stimulated guinea pig ileum and mouse vas deferens (10), thus supporting the hypothesis that glucose might interfere with morphine action on the opiate receptor.

Experimental evidence relating to the effect of diabetes on pain perception is contradictory. Chu et al. (11) reported a higher level of pain threshold in STZ-D male rats via the hot plate device. Likewise, Levine et al. (12) demonstrated prolonged tail-flick latencies to radiant heat in diabetic mice. On the other hand, Forman et al. (13) recently reported a significant reduction in the pain threshold of STZ-D female rats with the hot plate device. Morley et al. (14) demonstrated a lowered pain threshold in humans rendered acutely hyperglycemic by glucose injection but could not demonstrate a significant change in pain threshold of diabetic patients.

Diabetic rats display various changes of β-endorphin levels in different regions of the brain (13,15). The significance of these changes is not clear, although, considering the importance of opiates in pain control (16), these changes may be important in influencing pain perception.

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This study was undertaken to resolve aspects of the conflicting evidence, relating to the effect of hyperglycemia on pain perception, and to define the role of opiates in this process with greater clarity.

MATERIALS AND METHODS

Animals. Randomly bred Sabra rats from the Hebrew University breeding colony were housed in groups of six at 24°C with a 12-h light-dark cycle. Standard food pellets were available ad libitum. All experimental groups, unless otherwise specified, were supplied with water ad libitum.

Test for pain threshold. A 20 × 20-cm copper plate, surrounded by a 40-cm-high cage of transparent Plexiglas, was maintained at the desired temperature by circulating warm water through uniformly distributed tubing beneath the copper floor. Initially, the basal plate was insulated by a piece of cardboard. The animals were placed in a cage for a 1-min acclimatization period, after which the cardboard was withdrawn. The time was measured (by 2 observers) from the time the protective cardboard was removed to the time the animal licked one of its hind paws (hot-plate latency; HPL) or until 45 s had elapsed. If this response did not occur within 45 s, the animal was taken out, and the results were recorded as 46 s.

Induction of diabetes. The animals were rendered diabetic by injecting 50 mg/kg STZ (Sigma, St. Louis, MO) in saline buffered by sodium citrate to pH 4.0. Blood glucose levels were measured after 48 h with the glucose oxidase method. All animals with blood glucose levels <250 mg/dl were excluded from the experiments. Measurements of conduction velocity of action potentials in motor nerves (MNCV) were studied in six diabetic and age-matched control rats anesthetized with methoxyflurane and placed under a heat lamp to maintain body temperature. Stimulation was applied on the left sciatic nerve at the sciatic notch. Maximal stimuli at a frequency of 20 Hz were delivered from a Tektronix TM 501 stimulator. Evoked muscle potentials were obtained from the interosseous muscle with a unipolar electrode. The action potential amplitudes and the distal latencies were recorded from a Tektronix 5111 storage oscilloscope.

Experimental design. The baseline HPL of 20 rats was determined. The rats were then equally divided into four groups. The first group, receiving 0.14 mol/kg i.p. glucose in saline (vol 10 ml/kg), was compared with the second group, which received an intraperitoneal injection of pure saline in a similar volume. Measurement of HPL was recorded 15 min and 30 min after injection, after which blood samples were obtained from the tail vein to determine the blood glucose levels. At the end of this series, the experiment was repeated on the two remaining groups; one group received an intraperitoneal injection of saline, and the second group received glucose. The copper plate was maintained at 53 ± 1°C.

In acute diabetes, the HPL of 30 STZ-D rats was compared with that of 30 normal rats of the same age and weight 2, 3, 5, and 9 days after STZ injection. The animals were not treated with insulin.

In chronic diabetes, the HPL of 48 STZ-D rats was compared with that of 48 normal rats 20, 35, 55, and 120 days after STZ injection. Because these animals were not treated with insulin, the number of diabetic rats dwindled as the experiment progressed.

In acute diabetes, 12 STZ-D rats (10 days after injection) were selected on the basis of HPL < 10 s to study the analgesic effect of morphine. Twelve normal rats of the same age and weight were selected on the same basis. The temperature of the plate was raised slightly to 54 ± 1°C. In the first series, 6 diabetic rats followed by 6 normal rats received a 5-mg/kg s.c. injection of morphine hydrochloride in saline (vol 1 ml/kg). Measurement of HPL was repeated 15, 30, and 45 min after injection. The experiment was repeated on the second series of animals with 6 normal rats receiving the injection followed by 6 diabetic rats.

In chronic diabetes, 12 STZ-D rats (110 days after injection) with low baseline HPLs were compared with 12 young normal rats of the same weight (due to the weight differences caused by the diabetic process, it was not possible to compare animals of the same age and weight at this age). The experiment was then conducted as previously described.

Fourteen normal rats were kept on a glucose-saccharin cocktail ad libitum for 1 wk to induce the intake of large volumes of a sweet solution (17). The cocktail, containing 3% glucose and 6 mM sodium saccharin in deionized water, induces tolerance to the analgesic effect of a small dose of morphine within 24 h. The control group consisted of 15 normal rats of the same weight kept on deionized water ad libitum for 1 wk. The baseline HPL of the two groups at the end of 1 wk on sweet solution and after the injection of 5 mg/kg morphine was compared.

Calculations and statistical analysis. All results were recorded as HPLs. Because the measurement of the HPLs after morphine injection was assessed repeatedly during 45 min and the HPLs of the acute and chronic diabetic rats were measured repeatedly during 9 and 120 days, respectively, the differences between the mean of four measurements were analyzed with analysis of variance (ANOVA) for repeated measurements. The means of each group at each point is shown in the figures. The vertical lines represent 1 SE of the mean. Significant differences in HPLs between groups and the differences in HPLs after morphine injection at each point were determined by Student's *t* test.

RESULTS

The rats injected intraperitoneally with glucose had an average blood glucose level of 292 ± 41 and 224 ± 36 mg/dl 20 and 40 min after injection, respectively. Blood glucose levels 2 days after STZ injection was between 294 and 516 mg/dl (mean 363 ± 34 mg/dl). Mean blood glucose levels 20, 35, 55, and 110 days after STZ injection were 389 ± 18, 394 ± 17, 381 ± 16, and 402 ± 21 mg/dl, respectively. The mean weight of the diabetic rats 20, 35, 55, and 110 days after STZ injection was 205 ± 4.7, 212 ± 7.2, 232 ± 8.2, and 256 ± 7.9 g, respectively, compared to 222 ± 4.4, 276 ± 6, 303 ± 7.1, and 458 ± 11 g, respectively, in the normal age-matched rats. The MNCV 55 days after STZ injection was 44.1 ± 0.7 and 51.4 ± 0.9 m/s in the diabetic and normal age-matched rats, respectively ($P < .04$).

Figure 1 demonstrates the HPLs of the diabetic rats 2, 3, 5, and 9 days after STZ injection compared with the HPLs of age-matched control rats. One-way ANOVA with repeated measurements revealed a nonsignificant main effect for group factor [$F(1,51) = 1.42$, $P = .24$], a nonsignificant main

effect for repeated factor [$F(3,153) = 1.80$, $P = .15$], and a nonsignificant interaction between group and repeated factors [$F(3,153) = 0.26$, $P = .85$]. A t test to compare the mean HPLs of the two groups did not reveal any significant difference on each day of measurement.

Figure 2 demonstrates the HPLs of the diabetic rats 20, 35, 55, and 120 days after STZ injection compared with the HPLs of normal age-matched rats. One-way ANOVA with repeated measurements revealed a nonsignificant main effect for group factor [$F(1,49) = 0.12$, $P = .988$]. A significant main effect was found for the repeated factor [$F(3,147) = 6.1$, $P < .001$], but the interaction between group and repeated factors was nonsignificant [$F(3,147) = 0.27$, $P = .85$]. A t test to compare the mean HPLs of the two groups did not reveal any significant difference on each day of measurement.

Figure 3 demonstrates the mean HPLs of the glucose-injected rats, 15 and 30 min after injection, compared with the saline-injected rats. One-way ANOVA with repeated measurements revealed a nonsignificant main effect for group factor [$F(1,16) = 0.37$, $P = .55$]. A significant main effect was found for the repeated factor [$F(2,32) = 5.48$, $P < .05$], but the interaction between group and repeated factors was nonsignificant [$F(2,32) = 0.06$, $P = .94$]. The HPLs 15 and 30 min after injection were similar in both groups.

The influence of subcutaneous injection of morphine (5 mg/kg) on the HPLs of the diabetic rats 10 days after STZ injection compared with normal age-matched rats is presented in Fig. 4. One-way ANOVA with repeated measurements revealed a significant main effect for group factor [$F(1,22) = 7.41$, $P < .05$], a significant effect for the repeated factor [$F(3,66) = 21.1$, $P < .01$], and a significant interaction between group and repeated measurement factors [$F(3,66) = 5.43$, $P < .001$]. A t test to compare groups at each point revealed a significant prolongation of HPL in the normal rats compared with the diabetic rats 30 ($P < .05$)

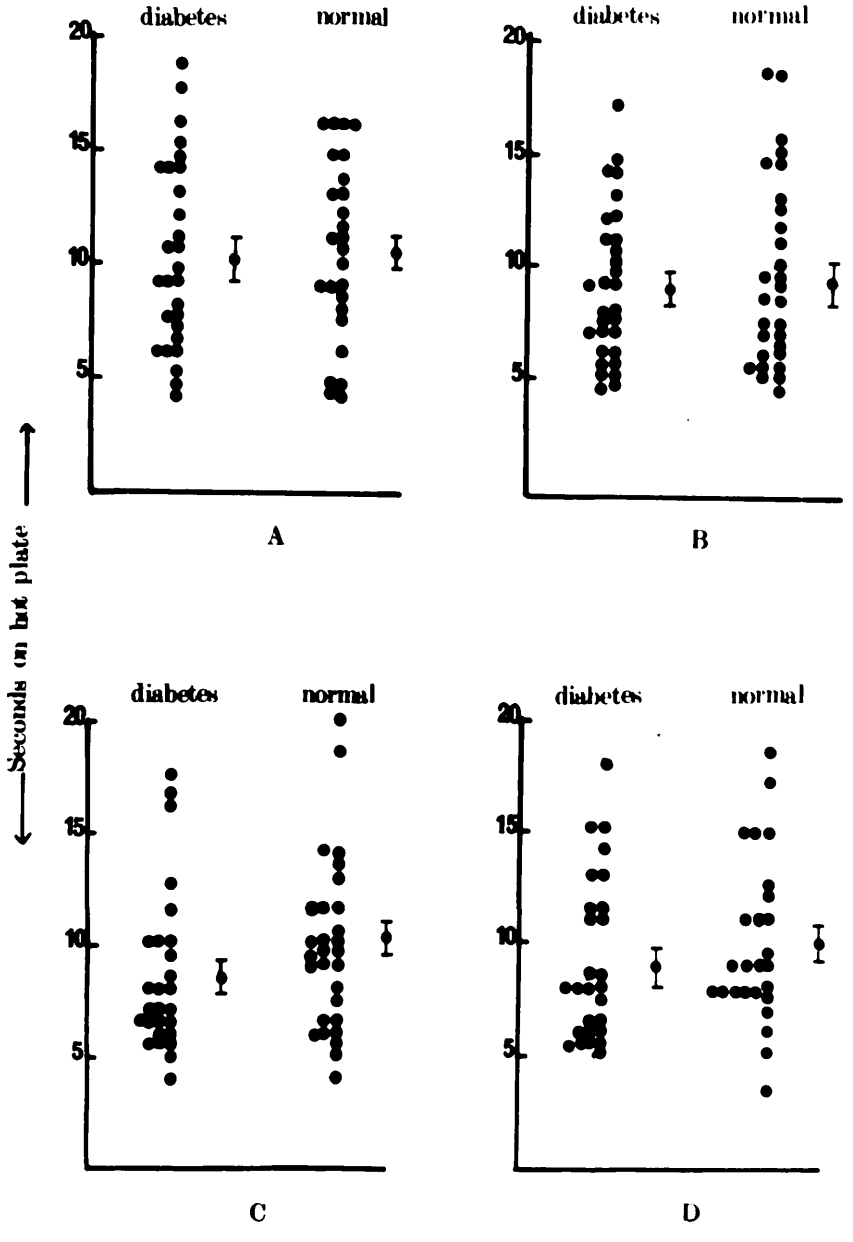

FIG. 1. Hot plate latency of normal and streptozocin (STZ)-induced acutely diabetic rats. *A*: 2 days after STZ injection. *B*: 3 days after STZ injection. *C*: 5 days after STZ injection. *D*: 9 days after STZ injection.

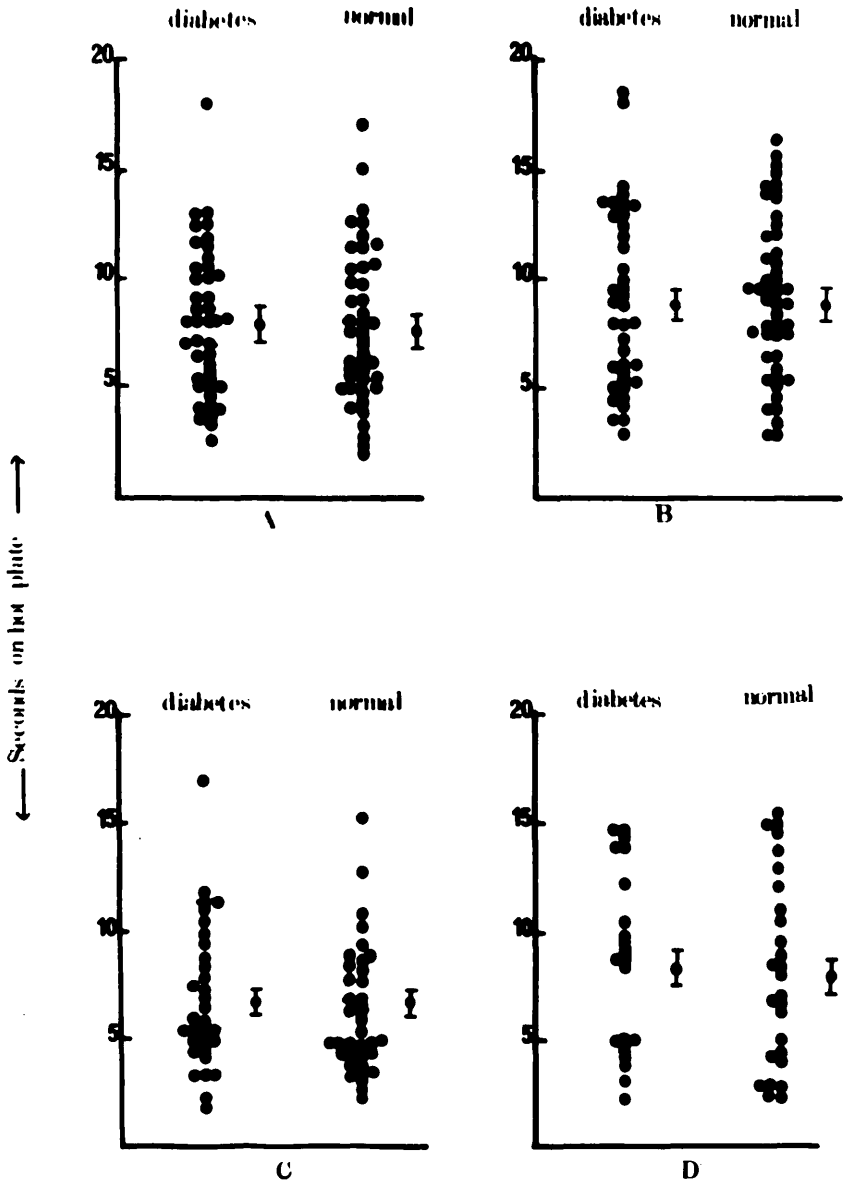

FIG. 2. Hot plate latency of normal and streptozocin (STZ)-induced chronically diabetic rats. *A*: 20 days after STZ injection. *B*: 35 days after STZ injection. *C*: 55 days after STZ injection. *D*: 110 days after STZ injection.

and 45 ($P < .01$) min after morphine injection. Figure 5 demonstrates the changes in mean HPL after injection of morphine (5 mg/kg) in diabetic rats 110 days after STZ injection compared with normal weight-matched rats. One-way ANOVA with repeated measurements revealed a significant main effect for group factor [$F(1,22) = 21.59$, $P < .01$], a significant main effect for the repeated measurement factor [$F(3,66) = 16.21$, $P < .001$], and a significant interaction between group and repeated measurement factors [$F(3,66) = 12.72$, $P < .001$]. A t test revealed a significant prolongation of HPL in the normal rats compared with the diabetic rats 15 ($P < .01$), 30 ($P < .001$), and 45 ($P < .01$) min after morphine injection.

The HPL of 14 rats treated with saccharin-rich deionized water for 7 days was compared with the HPL of another 15 age-matched rats receiving deionized water. The mean HPL of the saccharin group was 14.1 ± 1.8 s compared with 8.2 ± 0.9 s in the rats on pure water ($P < .05$) (Fig. 6). Figure 7 demonstrates the effect of morphine injection (5 mg/kg) on mean HPLs in the saccharin-supplemented group compared with the water-supplemented group. One-way ANOVA with repeated measurements revealed a significant main effect for group factor [$F(1,22) = 12.6$, $P < .01$], a significant main effect for the repeated measurement factor [$F(3,63) = 18.2$, $P < .001$], and a significant interaction between group and repeated measurement factors [$F(9,13) = 14.72$, $P < .001$]. A t test revealed a significant prolongation of HPL in the water-supplemented rats compared with the saccharin-supplemented rats 15 ($P < .01$), 30 ($P < .001$), and 45 ($P < .05$) min after morphine injection.

DISCUSSION

Our results indicate that in the male rat, neither an acute state of hyperglycemia, in the form of an intraperitoneal injection of glucose or acute STZ-D, nor chronic STZ-D, alters the pain threshold as determined by HPL. However, both acute and chronic states of STZ-D noticeably decrease the analgesic effect of morphine.

An experimental model of a glucose-saccharin cocktail, which is thought to enhance the release of endogenous

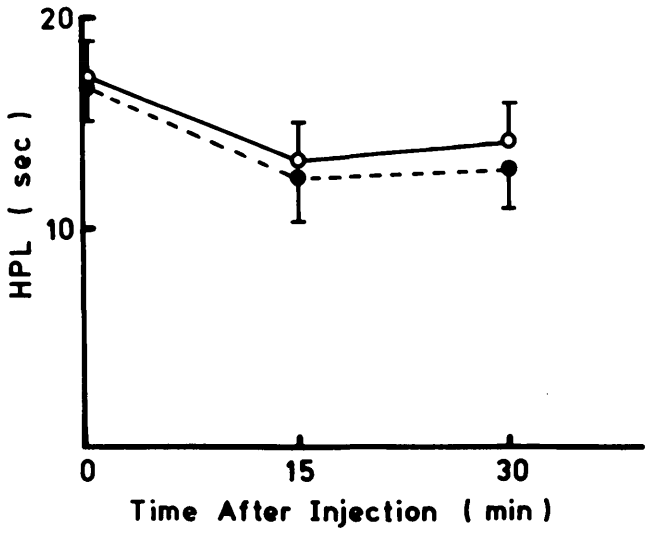

FIG. 3. Mean change in hot plate latency (HPL) of normal rats (n = 10) 15 and 30 min after injection of 0.14 mol/kg i.p. glucose (○) compared with age-matched rats (n = 10) injected intraperitoneally with similar volume of saline (●).

opioid peptides (EOPs) (18,19) is known to diminish the responsiveness of male Sabra rats to morphine (17). We found that this cocktail prolonged the HPL and at the same time opposed the analgesic effect of morphine, probably due to the enhancement of EOP secretion. A similar mechanism could explain the resistance to morphine in diabetes; diabetes might enhance the release of EOP, which blunts the ensuing analgesic effect of morphine. However, if this is true, a significant prolongation of the baseline HPL similar to that seen in animals supplemented with glucose-saccharin cocktail would also be expected in the diabetic state, contrary to our findings.

In 1981, Simon and associates (7,8) suggested that an antagonistic effect exerted by glucose on the opiate receptor could significantly diminish the ensuing effect of morphine. Later, Shook and Dewey (9) demonstrated that STZ-D rats and spontaneously diabetic mice were less susceptible to

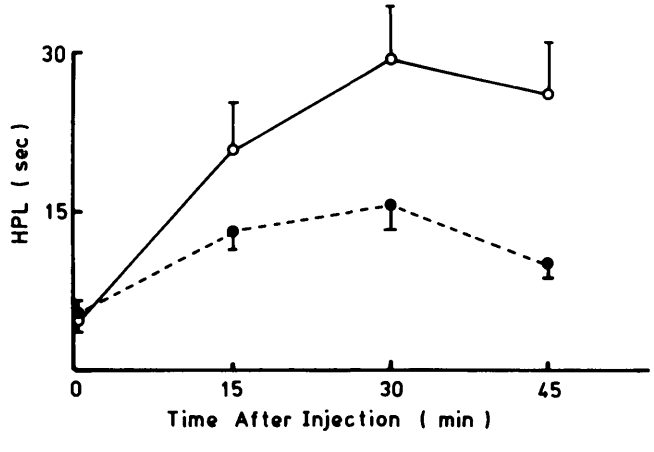

FIG. 4. Mean change in hot plate latency (HPL) of 12 acutely diabetic (●) rats (10 days after streptozocin injection) 15, 30, and 45 min after being injected with morphine (5 mg/kg) compared with 12 normal (○) aged-matched rats 15, 30, and 45 min after injection of morphine (5 mg/kg).

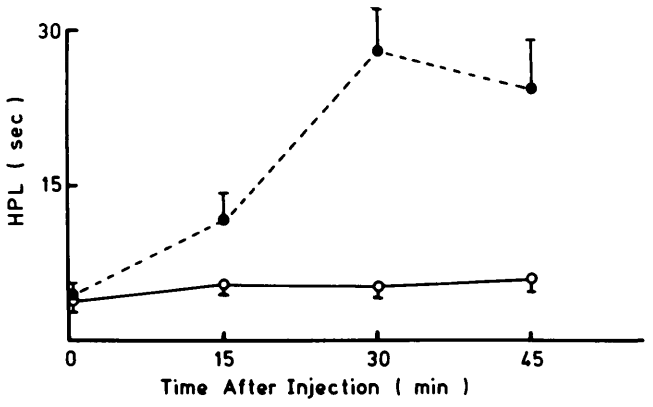

FIG. 5. Mean change in hot plate latency (HPL) of 12 chronically diabetic (○) rats (120 days after streptozocin injection) 15, 30, and 45 min after being injected with morphine (5 mg/kg) compared with 12 normal (●) weight-matched rats 15, 30, and 45 min after injection of morphine (5 mg/kg).

the development of physical dependence on morphine than their respective nondiabetic controls. They also demonstrated that high glucose concentration in vitro (400 mg/dl) decreased the potency of normorphine in the electrically stimulated guinea pig ileum and mouse vas deferens preparations, and attenuated the development of dependence on morphine in the isolated guinea pig ileum (10). These findings support the notion that hyperglycemia might diminish the analgesic effect of morphine by exerting a direct antagonistic effect on the opiate receptor. This effect could be the consequence of a decrease in receptor number, an alteration in the conformation of the opiate receptor, or, less likely, the result of interference with intracellular postreceptor effect. A preliminary report suggested that glucose may decrease the affinity of brain membrane receptors to ^3H but increase the number of binding sites (20).

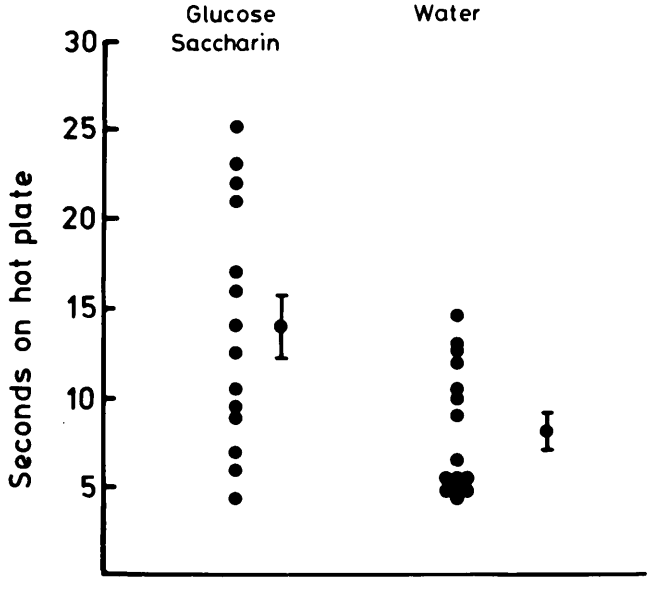

FIG. 6. Hot plate latency of normal rats kept on deionized water for 1 wk and of normal rats kept on glucose-saccharin solution in deionized water for 1 wk.

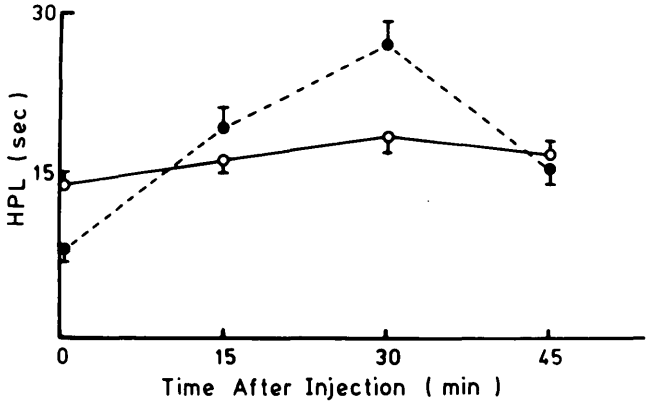

FIG. 7. Mean change in hot-plate latency (HPL) of 12 normal rats supplemented for 1 wk with saccharin-rich water (○) 15, 30, and 45 min after injection of morphine (5 mg/kg) compared with 12 normal age-matched rats supplemented with water (●) 15, 30, and 45 min after injection of morphine (5 mg/kg).

The antagonistic effect of glucose to morphine action on the opiate receptor in diabetic rats should also blunt the effect of EOP and result in shortened HPL, contrary to our findings. It might be that in our diabetic rats, the antagonistic effect of hyperglycemia was overcome by hypersecretion of endogenous peptides, such as β-endorphin.

Increases in β-endorphin levels in the cerebrospinal fluid have been shown to ameliorate pain perception (16). Different forms of β-endorphins predominate in different regions of the brain and are derived from a single precursor by differential processing (21). The only form possessing significant analgesic activity is the unprocessed form (22,23), whereas its related peptides are inert. The potent form of β-endorphins is predominant in the hypothalamus and the anterior pituitary (21); thus, removal of the pituitary gland in rats attenuates the EOP-induced analgesia but potentiates the analgesic response to morphine (24).

A significant elevation of β-endorphin concentration in the anterior pituitary of untreated STZ-D rats has been demonstrated by Forman et al. (13), whereas Locatelli et al. (15) did not demonstrate a significant change in anterior pituitary β-endorphin in rats with milder diabetes (15). On the contrary, β-endorphin concentration in the hypothalamus of the diabetic rats was found to be decreased in both studies. The reduced β-endorphin levels in the hypothalamus could be the result of increased secretion of β-endorphin, yet the above studies suggested that it was the result of a reduced production of β-endorphin in the hypothalamus due to the hypoinsulinemic state. Indeed, treatment with insulin resulted in increased β-endorphin concentration in the hypothalamus to a level higher than normal (15). Thus, in the diabetic rats, reduction of hypothalamic β-endorphin production and the hyperglycemic state should both result in a shortened HPL similar to the finding reported by Forman et al. (13). It might be that in our diabetic rats, a shortening of HPL due to these two mechanisms was compensated for by increased β-endorphin production in the anterior pituitary, resulting in unchanged HPL.

The entire issue is further complicated by the fact that the diabetic state tends to change the content and concentration of other products known to influence pain perception and opiate analgesia. Different manipulations of cholinergic neurotransmission (which might happen in diabetes) have been shown to alter the antinociceptive effects of opiate narcotics (25). Changes in the concentration of various neurotransmitters might influence nociception in diabetes. Striate catecholamines (especially dopamine) were found to be increased (11,26), whereas whole-brain tryptophan (27) and hypothalamic and midbrain serotonin concentrations were found to be decreased (11) in diabetic animals. Elevation of striate dopamine levels made rats less sensitive to painful stimuli (28), whereas depletion of brain serotonin levels made rats more sensitive to painful stimuli (29). Glucocorticoids known to blunt the action of β-endorphin are also generally elevated in the diabetic state (30). L-Pyroglutamyl-L-histidyl-L-prolinamide, cholecystokinin, and bombesin profoundly suppress food intake in diabetic mice compared with control, probably by modulation of opioid peptide action on the opiate receptor (31). The actions of substance P, which has been shown to alter the normal modulation of pain transmission in the spinal cord (32), dynorphin (33), and other peptides such as leucine and methionine enkephalin, which modulate β-endorphin analgesic effect and act as opioid agonist (34), are also influenced by the diabetic state. Somatostatin, which acts as a neurohormone regulating anterior pituitary function, is also known to block acetylcholine release and to participate as an inhibitor modulator for incoming pain (35). STZ-D rats have an increased number of δ-cells, with increased pancreatic somatostatin concentration; thus, somatostatin might also play a role in altered pain perception in diabetes.

Thus, we postulate that the diabetic state tends to decrease pain perception due to the antagonistic effect of glucose on opiate receptors and a decrease in hypothalamic β-endorphin synthesis and concentration. This effect might be countered by a compensatory increase in the synthesis and secretion of β-endorphin from the anterior pituitary and by the regulation of other pain-modulating peptides such as serotonin, dopamine, glucocorticoids, substance P, and somatostatin, resulting in a steady state.

How do these observations relate to diabetic neuropathic pain? It is conceivable that diabetic patients who experience neuropathic pain might lose their capability to cope with the antagonistic effect of glucose. It might be that the diabetic state in these patients causes β-endorphin depletion in the hypothalamus, which is not counterbalanced by increased β-endorphin in other regions such as the hypophysis, as was shown by Locatelli et al. (15), thus resulting in a decreased pain threshold. Insulin supplementation induces an elevation of β-endorphins in the hypothalamus (15) and might also influence other pain modulator peptides, thus relieving neuropathic pain, as was evident by the pain relief effect induced by the euglycemic state in diabetic subjects.

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