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# *High Doses of Spinal Morphine Produce a Nonopiate Receptor-mediated Hyperesthesia: Clinical and Theoretic Implications*

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**In rats with chronically implanted intrathecal catheters, high concentrations of morphine (3 μl of 50 mg/ml: 150 μg) yielded a reliable and striking syndrome of pain behavior that involved intermittent bouts of biting and scratching at the dermatomes innervated by levels of the spinal cord proximal to the catheter tip. In addition, during intervals between bouts of agitation, the animals displayed a clear, marked hyperesthesia where an otherwise innocuous stimuli (brush stroke) evoked significant signs of discomfort and consequent aggressive behavior. These effects were exaggerated rather than reversed by high doses of naltrexone. The effect, perfectly mimicked by a considerably lower dose of morphine-3-glucuronide (15 μg) or the glycine antagonist strychnine (30 μg), was not produced by equimolar concentrations of sodium sulfate, glucuronide, methadone, or sufentanil. In halothane-anesthetized cats, light brushing of the hindpaw and tail or low-intensity stimulation of the sciatic nerves resulted in prominent elevations in blood pressure and pupil diameter following the intrathecal administration of high concentrations (50 mg/ml; 0.1 ml) of morphine sulfate. This effect, exaggerated by naloxone, was produced by a lower concentration of intrathecal morphine-3-glucuronide (5 mg/ml; 0.1 ml) but not by intrathecal saline. These results suggest the possibility that the effects of high doses of morphine may be characterized by a nonopiate receptor-mediated effect that alters the coding of sensory information in the spinal cord. The authors speculate that high concentrations of spinal opiates, as may be employed in tolerant terminal-cancer patients, could exert an action that physiologically antagonizes the analgesic effects otherwise mediated by the action of morphine on the spinal opiate receptor. (Key words: Morphine-3-glucuronide. Spinal cord: pain coding. Spinal morphine: autonomic effects; nonopioid effects. Strychnine.)**

THE USE OF SPINALLY administered morphine in controlling pain in terminal cancer has been accompanied by reports of tolerance. This has led to the use of high doses of the opiate in which the daily infusion dose requires concentrations approaching the limit of the opiate solubility (*e.g.* around 65 mg/ml).[1–4] While the pharmacology of the effects produced by standard doses of spinal morphine (0.5–1 mg/1 ml intrathecal; 5–10 mg/10 ml epidurally) have been characterized as those of an opioid receptor,[5,6] the pharmacology of higher doses have not been examined. Previous studies have suggested that at high concentrations, spinal morphine results in signs of considerable agitation in animal models.[7] Because of the current clinical interest in high concentrations (50 mg/ml),§ we sought to examine the pharmacologic effects associated with such concentrations. In these experiments, we observed that these concentrations resulted in a profound agitation response that was associated with a clear hyperesthesia (allodynia). These effects were not antagonized by naloxone.

## Methods

### Animal Models

Rats were prepared with chronic, lumbar intrathecal catheters (polyethylene tubing, PE-10; 7.5 cm from cisterna to tip).[8,9] The animals received intrathecal injections in volumes of 3 μl followed by 10 μl of saline to flush the catheter. Each drug study was carried out with groups of four rats at a time. After injection, each animal was placed in a clear plexiglass box (8 × 15 × 15 cm), the floor of which was covered with sawdust.

To quantify the analgesic effects of spinal opiates, the hot plate was employed. Briefly, the animal was placed on a surface maintained at 52.5° C (21 × 16 cm) surrounded by a plexiglass wall 30-cm high. The latency to licking of the hindpaw or a jump in which both hindpaws were lifted from the surface was the measured endpoint. Failure to respond by 60 s resulted in a termination of the test and assignment of that score. All responses were converted to the per cent of the maximum possible effect (MPE) where:

$$\text{MPE} = \frac{\text{postdrug response latency} - \text{predrug response latency}}{60 - \text{predrug response latency}} \times 100$$

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To examine and quantify spontaneous agitation (SA) and the response to nonnoxious tactile stimulation (*e.g.*, a probe drawn lightly across the flank—touch-evoked agitation [TE]), a three-point rating scale was employed: 0 = no change/no effect of stroking; 1 = mild squeaking, occassional scratching or biting at the flank/mild squeaking, attempts to move away the stroking probe; 2 = vigorous squeaking, gnawing at flank leading to depilation, vigorous squeaking evoked by stroking probe, bites and chews on the probe. The presence or absence of SA was assessed in each animal during each 1-min interval and the TE at 5-min intervals, for the 50-min period after injection without prior knowledge of drug employed. For statistical comparisons between drug treatments, the SA and TE score for each animal was summarized over the total observation interval (50 min) and expressed as a percentage of the maximum possible score obtainable for the 50-min interval (SA = 50 × 2 = 100; TE = 10 × 2 = 20).

Cats were anesthetized and maintained with halothane (0.8% inspired: Fluotec® vaporizer). A tracheal cannula was placed and the animal was ventilated mechanically (Harvard® model 613) under pancuronium. Each animal was prepared with femoral arterial and venous lines and a lumbar intrathecal catheter and placed in a stereotaxic head holder. The lumbar intrathecal catheter (polyethylene tubing, PE-10; 27–30 cm in length) was placed through an incision in the cisternal membrane after a midline dissection. Blood gases were assessed periodically with an IL-113® blood gas analyzer using a femoral artery blood sample and maintained by ventilatory control within normal limits ($Pa_{O_2}$: 110–150 mmHg; $Pa_{CO_2}$: 37–39 mmHg; $pH_a$ = 7.38–7.42). Pupillary diameter was measured to the nearest millimeter periodically using a plastic ruler fixed in position before the eye. Pupil size was expressed as the percentage of maximum diameter observed at death. Blood pressure was continuously measured.

To examine the role of large and small afferents, some cats were also prepared with bilateral sciatic nerve electrodes. Stimulation (100–1500 μA; 1.0 ms pulse, 50 Hz, 1 s pulse train, 0.5/s) given bilaterally (Grass S-88® stimulator; PSIU-6 constant current isolation units). Prior to the administration of muscle relaxant, the minimum threshold current at either nerve that produced a motor twitch in the respective leg was determined. From previous studies in which we recorded distally from the sural nerve, we determined that stimulating at three times the motor threshold evoked resulted in a compound action potential that traveled at 30–120 m/s. At intensities 15–20 times the motor threshold, a complex waveform including the initial rapid peak was observed along with activity that traveled at less than 2 m/s. Because of their respective association with conduction velocity and stimulus intensity, these are referred to as Aβ and Aβ/Aδ/C, respectively.

### Drugs

Morphine sulfate (Merck); morphine-3-β-D-glucuronide (Sigma); naltrexone-HCl (Endo); strychnine-HCl (Sigma); and sodium sulfate (Sigma) were dissolved in sterile saline and delivered in 0.1 ml (cats) and 3 μl (rats), unless otherwise indicated. The *p*H of all solutions is titrated to 6.5 by 0.01 N NaOH or 0.01 N HCl. To control for the tonicity of high concentrations of morphine, equiosmolar solutions of sodium chloride were prepared. Using a vapor pressure osmometer (Wescor®, model 5700B) the osmolarity of a solution of 50 mg/ml morphine is 407.5 ± 5.7 mosm (μ ± SD, n = 5 determinations).

To examine whether the effects of high-dose morphine were altered in morphine-tolerant animals, rats with intrathecal catheters were implanted under halothane anesthesia with a morphine sulfate pellet (75 mg) on day 1 and a second pellet on day 3. On day 5, the effect of intrathecal morphine was examined. Previous studies have shown this paradigm to result in a significant loss of analgesic effect of intrathecal morphine in rats.[10]

## Results

### Rats

The intrathecal administration of morphine (150 μg/3 μl) reliably resulted, after a latency of 1–3 min, in a syndrome characterized first by bouts of severe SA, in which the rat bit and vigorously scratched the skin at or below the dermatome of the cord segments nearest the catheter tip (T12–L1). Each SA bout would last 10-30 s. Between bouts, the animal would sit or lie on its side and breathe heavily. The rat, however, was not depressed and it had clearly not lost its righting reflex. No evidence of respiratory or behavioral depression was noted during the first 50–60 min. Secondly, during the period between SA bouts, a prominent agitation response was evoked by a nonnoxious stimulus (allodynia). Thus, in the latter case, gentle stroking of the fur with the point of a pencil in the caudal aspects of the body, but not the face, evoked a vigorous squeaking and a coordinated attack on the stroking probe. Such reactive behavior was not elicited by the probe unless the animals were touched or gently stroked. This behavior is clearly distinguished from seizures, or a centrally organized spontaneous pain stimulus (as generated by intrathecally administered, excitatory amino acids, substance P, or capsaicin[9,11]) in that there is an apparent, organized attack–escape response evoked by the otherwise innocuous mechanical distortion of the

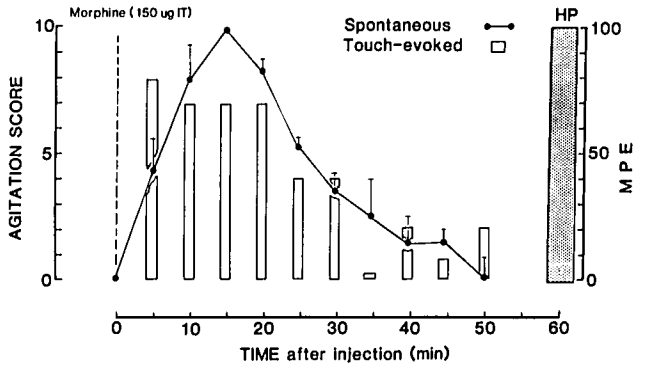


FIG. 1. Response of a group of four rats to intrathecal morphine (150 μg/3 μl) given at time 0. To demonstrate the time course of the effect, data are presented as mean ± SE of the spontaneous agitation score (● —— ●) cumulated over each 5-min interval. (Maximum possible score for each rat is 5 min × 2 = 10.) For the touch-evoked score, the cumulative score at each measurement time for all four animals is presented. (Maximum score: 4 rats × 2 = 8.) The hot plate response (MPE) was completely blocked at 60 min. For statistical analysis, see table 1. Other details are as described in the text.

hair or skin. As shown in figure 1, peak activity after intrathecal morphine in a typical group of rats receiving 150 μg morphine was observed at 10–15 min, and both TE and SA essentially disappeared by 50 min. At 60 min, as measured by the hot-plate response, the animal was clearly analgesic. Testing at earlier intervals was not feasible due to the reactivity of the animal. Tables 1 and 2 summarize the results obtained in the present series of experiments examining the effects of several intrathecally administered agents. Based on these results, the following points can be made.

1. This observed behavioral syndrome occurred at doses about ten times the dose of morphine required to produce a complete block of the hot-plate response in the rat (150 *vs.* 15 μg/3 μl: table 1).

2. The phenomena, unlike the analgesic effects, are not reversed even by large doses of antagonist (naltrexone: 30 mg/kg). The co-administration of antagonist with high-dose morphine exaggerated the TE and SA measures but blocked the HP (table 1).

3. The algogenic effects, in contrast to the analgesic effects of high concentrations of intrathecal morphine, are not diminished in animals rendered tolerant by the implantation of morphine pellets (table 1).

4. Other opiates such as methadone and sufentanil, at doses up to 40 times their $ED_{100}$ or the limit of solubility, evoked significant analgesia, but failed to evoke comparable hyperesthetic or algogenic effects (table 1).

5. To determine whether these effects were associated with morphine and not the salt or the *p*H/osmolarity of the agent, injections of equimolar doses of sodium sulfate, sodium glucuronide, or osmolarity-matched solutions of sodium chloride failed to produce the observed effects (table 2).

6. Morphine-3-β-D-glucuronide at 1/10 the concentration of morphine evoked a syndrome that was indistinguishable from that produced by morphine, but did not produce analgesia. The effects of morphine-3-β-D-glucuronide were suppressed by low analgesic doses of intrathecal morphine (15 μg) (table 2).

7. Strychnine evoked an identical syndrome of comparable magnitude. This effect was significantly antagonized by analgesic doses of intrathecal morphine (table 2).

## CATS

To determine if the previously mentioned phenomena had a corollary in another species, we examined the effects

TABLE 1. Summary of Effects of Intrathecal Agents in the Rat on the Spontaneous Agitation (SA), Touch-evoked Agitation (TE), and Hot-plate Response Latency

| Intrathecal Drug | n | SA Score* | TE Score* | Hot-plate Response† |
|---|---|---|---|---|
| Saline | 4 | 0 ± 0 | 0 ± 0 | 18 ± 3 |
| Morphine (150 μg/3 μl) | 8 | 47 ± 8‡ | 56 ± 9‡ | 100 ± 0‡ |
| Morphine (15 μg/3 μl) | 4 | 0 ± 0 | 0 ± 0 | 100 ± 0‡ |
| Morphine (150 μg/15 μl) | 4 | 41 ± 6‡ | 49 ± 8‡ | 100 ± 0‡ |
| Morphine (150 μg/3 μl) + naltrexone (30 mg/kg ip) | 4 | 69 ± 6‡§ | 79 ± 8‡§ | 23 ± 12§ |
| Morphine (150 μg/3 μl) + morphine pellets (150 mg/5 days)¶ | 4 | 54 ± 12‡ | 72 ± 6‡§ | 33 ± 12§ |
| Sufentanil (150 μg/3 μl) | 4 | 0 ± 0 | 0 ± 0 | 100 ± 0‡ |
| Sufentanil (150 μg/3 μl) + naltrexone (1 mg/kg, ip) | 4 | 0 ± 0 | 0 ± 0 | 19 ± 5§ |
| Methadone (100 μg/3 μl) | 4 | 0 ± 0 | 0 ± 0 | 100 ± 0‡ |
| Methadone (100 μg/3 μl) + naltrexone (1 mg/kg, ip) | 4 | 0 ± 0 | 0 ± 0 | 22 ± 6§ |

* μ ± SD; see text for description of measurement technique.
† Assessed at 60 min; values are MPE (μ ± SD).
‡ $P < 0.05$ as compared with saline control, unpaired *t* test.
§ $P < 0.05$ as compared with agonist-alone condition.
¶ Two pellets containing 75 mg morphine sulfate were implanted subcutaneously, one on day 1 and one on day 3. Animals were tested on day 5.

TABLE 2. Effects of Intrathecal Nonopiate Agents in the Rat on the Spontaneous Agitation (SA), Touch-evoked Agitation (TE), and Hot-plate Response

| Intrathecal Drug | n | SA Score* | TE Score* | Hot-plate Response† |
|---|---|---|---|---|
| Morphine-3-glucuronide (3 μg/3 μl) | 4 | 49 ± 6‡ | 68 ± 8‡ | 19 ± 3 |
| Morphine-3-glucuronide (3 μg/3 μl) + morphine (15 μg/3 μl) | 4 | 13 ± 9§ | 26 ± 11§ | 68 ± 8§ |
| Strychnine (10 μg/3 μl) | 8 | 68 ± 14‡ | 51 ± 9‡ | 8 ± 3 |
| Strychnine (10 μg/3 μl) + morphine (15 μg/3 μl) | 4 | 18 ± 6§ | 26 ± 7§ | 48 ± 11§ |
| Sodium glucuronide¶ (1.5 μg/3 μl) | 4 | 0 ± 0 | 0 ± 0 | 12 ± 7 |
| Sodium sulfate¶ (26 μg/10 | 4 | 0 ± 0 | 0 ± 0 | 6 ± 4 |
| Sodium chloride** (36 μg/3 μl) | 4 | 0 ± 0 | 0 ± 0 | 10 ± 4 |

* $\mu \pm$ SD; see text for description of measurement technique.
† Assessed at 60 min. Values are MPE ($\mu \pm$ SD).
‡ $P < 0.05$ as compared with saline control, unpaired $t$ test; see table 1.
§ $P < 0.05$ as compared with agonist dose alone, unpaired $t$ test.
¶ Concentrations are equimolar to the high dose of the respective base.
** Concentration is equiosmatic to morphine sulfate 50 mg/ml.

of high concentrations of spinal morphine in halothane-anesthetized, normotensive cats (mean arterial blood pressure [MAPB]: 111 ± 7 mmHg; $Pa_{CO_2}$: 36 ± 3; $Pa_{O_2}$: 111 ± 4, $pH_a$: 7.421 ± 0.007).

Figure 2 presents a sequence of blood pressure tracings obtained in a single cat during brushing of the hindpaw, pinching with a pair of Kelly forceps of the hindpaw, and stimulation at the sciatic nerve during control, 30 min after the administration of intrathecal morphine (50 mg/ml; 0.1 ml) and then after the intravenous injection of naloxone (1 $mg \cdot kg^{-1} \cdot ml^{-1}$ iv). As indicated, under control conditions, brushing or stimulating the nerve at intensities three times threshold, evoking Aβ fiber activity, had no effect on pupil diameter or resting blood pressure. Strong forcep-pinch or sciatic stimulation at 20 times threshold, evoking activity in Aβ/Aδ/C fibers, reliably resulted in a significant elevation in blood pressure and a stimulus-dependent pupillary dilation (see table 3). The intrathecal administration of high concentrations of morphine sulfate resulted in an extremely prominent autonomic response to the previously ineffective brush and Aβ stimulation. After the administration of naloxone (1 mg/kg), there was no inhibition of the effects of intrathecal morphine on the autonomic responses evoked by brush or Aβ stimulation. Inspection of fig. 2 suggests that the effects were facilitated not only in magnitude, but also in the duration of the poststimulus effect.

Although resting blood pressure after concentrated intrathecal morphine was frequently not changed, all animals displayed small transient increases in blood pressure (see fig. 2). In two of six animals receiving high concentrations of intrathecal morphine, however, sustained increases in MABP of 20–40 mmHg were observed.

As indicated in table 3, comparable effects were produced by morphine-3-glucuronide at one-tenth the dose of morphine sulfate. Although by inspection there appeared to be a slight facilitation by naloxone (1 mg/kg, iv), the effects of morphine-3-glucuronide were not statistically altered by treatment with the naloxone even though the likelihood of a plateau effect obscuring such differences appears likely. Intrathecal saline had no detectable effect on either the resting MABP/pupil size or the changes in these measures evoked by the respective stimuli (see table 3). Naloxone (1 mg/kg) given intravenously had no effect on the response to brushing but served to facilitate in a small but statistically significant fashion the response to pinch and Aβ/Aδ/C stimulation.

In a few experiments not shown here, we observed that these effects of intrathecal morphine were not antagonized by naltrexone in doses up to 30 mg/kg, iv (n = 2).

Importantly, the ability to evoke this autonomic hyperreactivity, as in the rat, was somatotopically organized. Figure 3 presents typical results in a single animal. Thus, the ability at 30 min to evoke the marked hyperreactivity was initially observed only by brushing of the S4–L5 dermatomes. During the next 2 h, the effective zone spread to include the body regions as far rostral as T12–L1 (data not shown).

## Discussion

These observations suggest that in two species a high concentration of morphine (50 mg/ml), given intrathecally as a bolus may possess pharmacologic properties that differ from those associated with conventional doses of morphine. This effect is largely manifested on somatic input that are mediated by rapidly conducting afferents with low electrical thresholds and activated by light tactile stimulation. The effect is somatotopically organized, with the effective stimuli being those applied to the dermatomes innervated by the portions of the spinal cord acted on by the intrathecal agent. Significantly, the blood pressure and pupil response evoked by cutaneous pinch were, in contrast to the effect of brushing, only mildly exaggerated. (The residual effects might be accounted for by the tactile stimulation of the forceps and not the pinch.) The phenomenon thus presents uniquely as a spinally or-

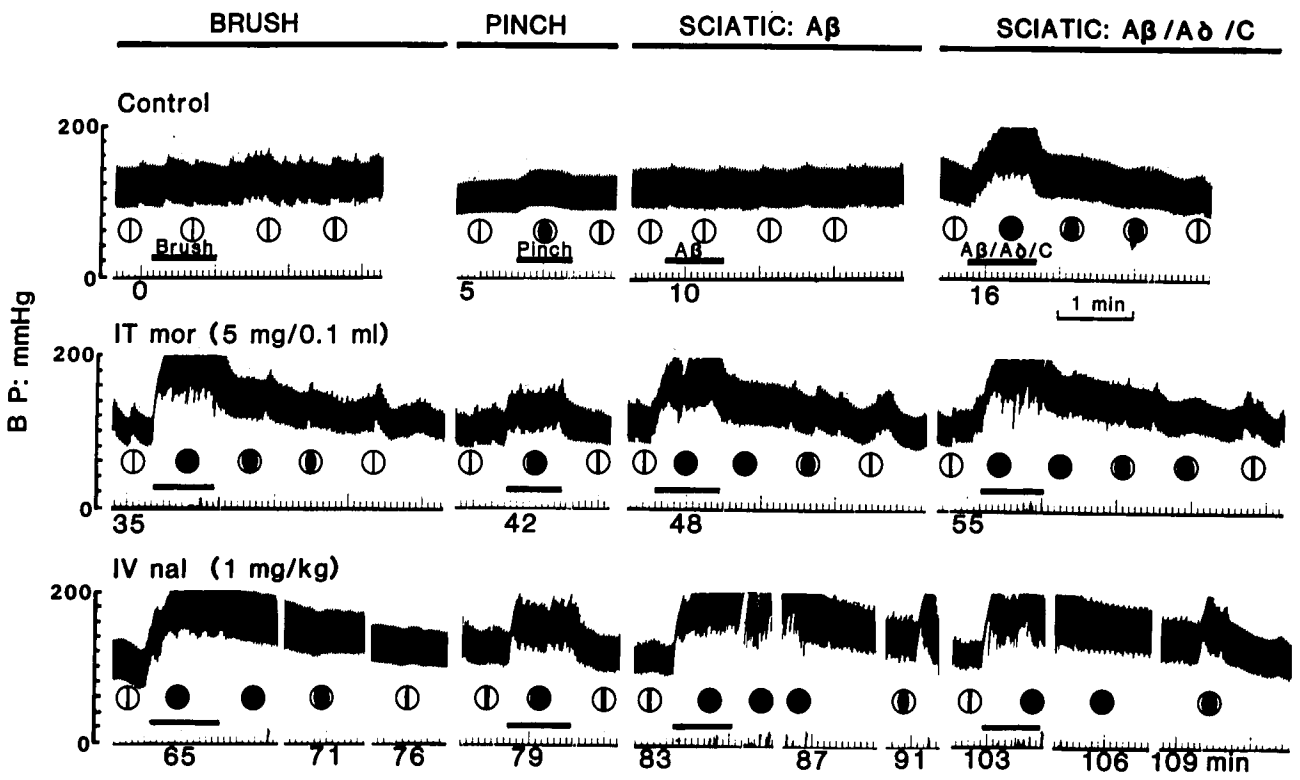


FIG. 2. Sequential blood pressure records obtained from a single cat before drug treatment (*upper*); 15 min after (*middle*) the intrathecal administration of morphine sulfate (50 mg/ml; 0.1 ml) and then 5 min after (*lower*) naloxone (1 mg/kg, iv). The number under each tracing indicates the time after the start of the experiment (*e.g.*, morphine was injected at 20 min and naloxone at 60 min). Under each condition the effect of brush and pinch applied to the hindpaw and bilateral sciatic nerve stimulation is at Aβ; and Aβ/Aδ/C fiber intensity is examined. The *insets* show the relative diameter of the right pupil at the time indicated. Other details of the preparation are as described in the text.

ganized allodynia (a painful event evoked by an innocuous stimulus).

With regard to the pharmacology of the effect, the phenomenon observed in the present studies is clearly dose dependent. Reducing the concentration by a factor of five (*e.g.*, 10 mg/ml), while holding the total dose constant, appeared to produce a small reduction in effect. As the SA/TE, unlike the antinociceptive actions, are not antagonized by naloxone or naltrexone and are not produced by sufentanil or methadone, it is clear that the effects are not produced by an action at an opioid receptor. On the other hand, as antagonists and morphine tolerance appeared to exaggerate the response, we believe that the analgesic effects of morphine at functional, nontolerant opioid receptors will physiologically antagonize some of the hyperalgesic properties of the drug at high concentrations. It should be stressed, however, that the effect is not due to a general physicochemical property of the injection solution. Thus, control injections of solutions matched for salt, *p*H, or osmolarity failed to exert an effect.

The mechanisms underlying these actions are not known, but three alternatives appear relevant.

First, it is known that during antagonism of acutely administered opiates, some degree of hyperreactivity may occur. As indicated, in table 1, no comparable signs were observed even after high doses of sufentanil and methadone.

Second, as indicated by Woolf[7] and ourselves, a metabolite of morphine, morphine-3-glucuronide, was observed to evoke an identical syndrome at a dose one-tenth that required for morphine. It may be possible that an uncommon metabolite of morphine may thus reach sufficient concentrations to be pharmacologically active in the presence of high doses of substrate, *e.g.*, morphine. The phenomenon has a clear structure–activity relationship requiring the morphine conjugate. Thus, sodium glucuronide was without effect at equimolar concentrations. Significantly, although there are no systematic studies in the brain to support this conclusion, the structure of sufentanil and methadone suggests that neither is as susceptible to conjugation as morphine (see refs 12 and

TABLE 3. Effects of Intrathecal Morphine Sulfate, Morphine-3-Glucuronide, or Saline on the Autonomic Responses Evoked by Brush, Pinch, and Sciatic Nerve Stimulation in Cats

| Intrathecal Drug | Stimulus | n | Pre-drug Control | | IT Drug | | IV Naloxone | |
|---|---|---|---|---|---|---|---|---|
| | | | ΔBP* | Pupil† | ΔBP | Pupil | ΔBP | Pupil |
| Morphine (5 mg/0.1 ml) | Brush | 6 | −6 ± 9 | 6 ± 3 | 48 ± 5§ | 91 ± 4§ | 51 ± 9 | 93 ± 5 |
| | Pinch | 6 | 21 ± 7‡ | 26 ± 11‡ | 36 ± 8 | 51 ± 7§ | 68 ± 13¶ | 72 ± 8¶ |
| | Aβ | 6 | 1 ± 8 | 2 ± 3 | 58 ± 9§ | 94 ± 2§ | 68 ± 11 | 98 ± 3 |
| | Aβ/Aδ/C | 3 | 39 ± 12‡ | 59 ± 12‡ | 61 ± 7§ | 98 ± 2§ | 61 ± 12 | 98 ± 2 |
| Morphine-3-glucuronide (0.5 mg/0.1 ml) | Brush | 4 | 2 ± 8 | 4 ± 3 | 41 ± 18§ | 89 ± 6§ | 52 ± 5 | 94 ± 3 |
| | Pinch | 4 | 18 ± 6‡ | 15± 3‡ | 21 ± 11 | 38 ± 11 | 27 ± 8 | 68 ± 9¶ |
| | Aβ | 4 | −2 ± 5 | 2 ± 6 | 52 ± 12§ | 89 ± 10§ | 58 ± 9 | 98 ± 1 |
| | Aβ/Aδ/C | 4 | 32 ± 9‡ | 48 ± 9‡ | 68 ± 15§ | 96 ± 2§ | 62 ± 15 | 97 ± 2 |
| Saline (0.1 ml) | Brush | 3 | 0 ± 3 | 0 ± 0 | 0 ± 6 | 0 ± 0 | 0 ± 8 | 0 ± 0 |
| | Pinch | 3 | 26 ± 8‡ | 25 ± 7‡ | 28 ± 9 | 28 ± 6 | 39 ± 9 | 36 ± 5 |
| | Aβ | 6 | 9 ± 2 | 5 ± 2 | 11 ± 5 | 8 ± 7 | 15 ± 8 | 16 ± 6 |
| | Aβ/Aδ/C | 3 | 42 ± 8 | 56 ± 11‡ | 39 ± 9 | 68 ± 11 | 46 ± 15 | 63 ± 9 |

* Maximum change in MABP as compared with the immediate prestimulus condition.

† Per cent of maximum pupil diameter as measured at death.

‡ $P < 0.05$ as compared with prestimulus levels.

§ $P < 0.05$ as compared with predrug control response.

¶ $P < 0.05$ as compared with IT agonist alone.

13). These agents did not result in allodynia at the highest doses used.

Third, it is known that high doses of morphine may produce antiglycinergic effects at spinal neurons.[14,15] Importantly, in the present work comparable signs of hyperesthesia were obtained with low doses of strychnine, a glycine-receptor antagonist. Glycine has been shown to mediate a postsynaptic inhibition on dorsal horn neurons. Removal of this input leads to prolonged activity in response to limited stimulation.[16] Denny-Brown *et al.*[17] observed that low doses of strychnine would increase the size of the somatic dermatome of a given spinal segment.

From a theoretic perspective these observations suggest that stimuli evoked by afferents with low electrical thresholds that are conventionally excited by light tactile stimulation will evoke a sensory message of the spinal cord level interpreted by the animal as pain. Significantly, previous psychophysiologic studies have shown that stimulation of afferents with low electrical thresholds for excitation (*e.g.*, large fibers) will indeed evoke sharp, stinging pain in human volunteers,[18] while the frequency of activity in ventrolateral tract fibers co-varies with the intensity of the stimulus and the magnitude of the pain segment in patients preparing to undergo percutaneous chordotomy.[19] These observations are consistent with the previous observation that strychnine promotes repetitive activity in spinal neurons that are excited by afferent input. It is significant that C-fiber afferents routinely result in repetitive activity in spinal dorsal horn neurons, which also receive Aβ input.[20] Jointly, these observations suggest that input that generates high-frequency, repetitive firing of these wide dynamic range (WDR) neurons may evoke a spinofugal message interpreted at the supraspinal level

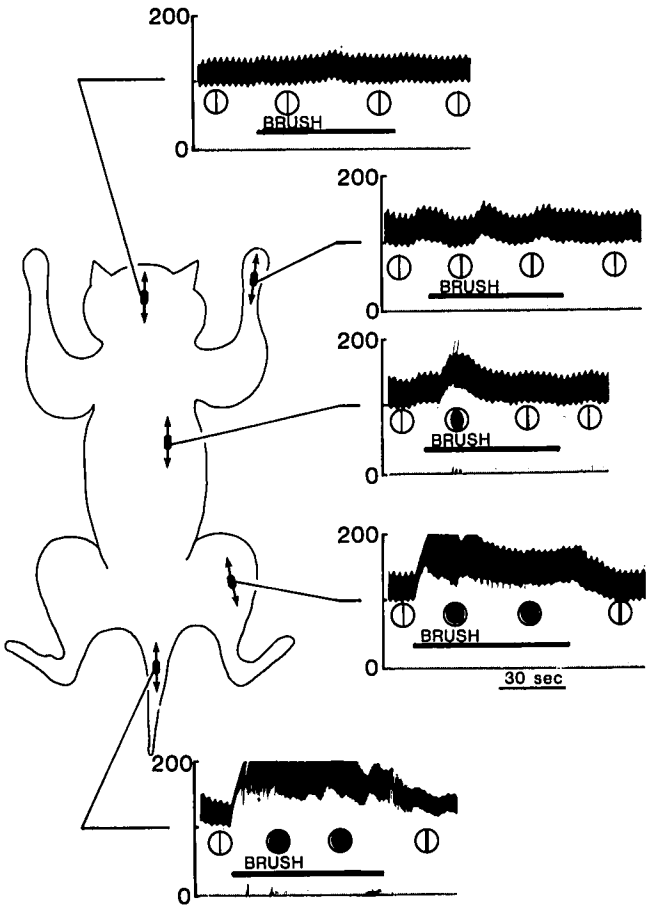


FIG. 3. Blood pressure records from a single cat indicating the effects produced by light stroking of the skin in the region indicated, carried out 15 min after the IT injection of morphine sulfate (50 mg/ml, 0.1 ml). *Insets* in each tracing show the relative pupil size at the time indicated.

as pain. Significantly, spinal agents that reduce the postsynaptic activity of these cells, such as morphine (present study) or delta-receptor agonists and alpha$_2$-agonists (TL Yaksh and GJ Harty, in preparation) will diminish the pain response.

Whether these somatic and autonomic phenomena are relevant to the actions of opiates given in high concentrations in humans is not known. Two points should, however, be noted.

First, moderate to severe pruritus has been reported in humans after spinal opiates, particularly morphine, have been administered. Unlike the present phenomenon, however, this effect appears reversible by naloxone.[21]

Second, while patients may go for long periods of time with relatively low doses of spinal opiates,[22] once the dose of spinal opiates required to produce pain relief begins to rise, the escalation may become very rapid.[2-4,23] There often appears to be no clear upper-dose plateau with spinally administered morphine, once dose requirements begin to rise. We speculate that in patients in whom morphine tolerance has occurred, high doses may indeed produce some degree of analgesia, but at these higher concentrations, the nonopiate, receptor-mediated, hyperalgesic effects of morphine demonstrated in the rat and cat models may begin to appear. Discontinuing the morphine administration would remove the source of the hyperesthesia, but in addition would uncover the pain syndrome that caused the physician to turn originally to opiates. This does *not* mean that tolerance is the result of an anomolous hyperesthesia secondary to a metabolite, rather that as tolerance progresses, higher doses are required and concentrations of spinal morphine are reached where effects mediated by nonopiate receptors become dominant.

Recently, unexpected hyperalgesic responses have been observed in terminal cancer patients receiving high concentrations of spinal morphine (35–120/3 ml $\cdot$ mg$^{-1}$ $\cdot$ day$^{-1}$) by infusion.¶ Anecdotally, at the Mayo Clinic, a patient suffering from an extensive chordoma received spinal opiates by infusion over a 2-yr period. After the initial 4–6-month period, the patient would periodically begin to develop increasing pain. Cessation of the infusion of morphine (3–5 mg/day) would frequently bring considerable, but incomplete, pain relief for 1–2 weeks, at which time the pain would return. Reinstitution of morphine infusion at a lower dose would again produce a state of analgesia.[24] Although these concentrations are relatively low, we believe the possibility that altered cerebrospinal fluid distribution and, therefore, dilution of the infused agent in a patient with changes in the morphology of the spinal space is a point of consideration.

It should be stressed that these observations in animal models do not necessarily preclude the clinical use of high concentrations of opiates. These results were obtained with bolus injections and in many instances patients receive opiates by infusion. As noted previously, the pharmacology of the present allodynic effects emphasizes the absolute need for high concentrations. If the phenomenon is mediated by a receptor (*e.g.*, glycine), then to the degree that diffusion and dilution occur, the phenomenon will diminish. If the effect is due to a metabolite, *e.g.*, morphine-3-glucuronide, then the effect will depend on the total dose of the parent compound as well as the rate of synthesis and rate of clearance of the metabolite. In this case, the glucuronide tends to be extremely polar and is likely cleared only slowly, leading potentially to its accumulation. We thus seek to alert the clinician to the fact that high concentrations of morphine do not simply mean more activity at an opioid receptor, but may in fact serve to bring into play drug effects that are independent of an opioid receptor, *i.e.*, at high concentrations morphine behaves as another drug. In this particular case, an unfortunate consequence of high concentrations of morphine appears to be a significant hyperesthesia. Because of the variable role of diffusion and dilution, we cannot propose a maximum usable concentration in humans, even though the likelihood of these effects appears in all test systems at concentrations of 50 mg/ml. We note that at the concentrations thus far examined, certain opiates such as sufentanil and methadone do not appear to possess these characteristics.

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