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The Medullary Dorsal Horn

A Site of Action of Morphine in Producing Facial Scratching in Monkeys

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Background: **Pruritus is a common side effect of epidural and intrathecal morphine administration in humans. This naloxone-reversible pruritus is typically present on the trunk, but is often severe around the eyes and nose, of the patients. The brain stem has been proposed as the site where opioids act to produce this effect. The authors studied the effect of morphine administered into the medullary dorsal horn (MDH), the brain stem homologue of the spinal dorsal horn, on facial-scratching behavior in monkeys.**

Methods: **Morphine was unilaterally microinjected into the MDH of rhesus monkeys. Systemic injections of the opioid-receptor antagonist naloxone (0.5 mg/kg intramuscularly) were also made in combination with morphine microinjection. Systemic injections of the antihistamine chlorcyclizine (1.0 and 2.5 mg/kg intramuscularly) were also made to determine if facial scratching was mediated through histamine release. The monkeys were videotaped for 10–15 min before and 1–2 h after opioid microinjection, and the number and location of scratches were counted.**

Results: **A dose-response curve was established for the μ/δ-opioid-receptor agonist morphine (0.5, 1.0, 2.5, and 5.0 μg). Specificity of the site of action within the MDH was examined by systematically changing the microinjection site, and examining the area of the face that the monkeys scratched. Morphine produced large dose-dependent increases in facial scratching ipsilateral to the microinjection. Increases in facial scratching were also observed contralateral to the microinjections. These effects were reversed by naloxone. The facial area scratched after microinjection of morphine was directly related to the injection site, with 1-mm changes in the location of the microinjection resulting in pronounced changes in the area of the face that the monkeys scratched. Systemic injection of chlorcyclizine produced only a small, transient attenuation of morphine's effect.**

Conclusions: **Data from this study demonstrate that the MDH is a site where morphine acts to produce facial scratching in monkeys by acting at opioid receptors. It is also likely that the MDH is a site where centrally administered opioids act in producing facial pruritus in humans. The effects of morphine on facial-scratching behavior were only modestly attenuated with chlorcyclizine, indicating a minor involvement of a histamine-dependent mechanism of action. (Key words: Analgesics, opioid: morphine. Antagonists, opioid: naloxone. Complications: pruritus. Nerve: trigeminal.)**

EPIDURAL and intrathecal spinal cord administration of opioids in humans can produce pruritus and the associated scratching behavior.[1,2] This pruritus and scratching are, typically, first manifested at the segmental level of the trunk that corresponds to the level of the injection. Over the course of several hours, the pruritus and scratching can migrate up the trunk to the face.[3,4] This facial pruritus and scratching is sometimes severe, with the primary locus being around the eyes and nose.[5–7] It is obtained at relatively low dosages of opioids and is reversed by the opioid antagonist naloxone.[3]

In the current study, we examined the effects of microinjecting morphine into the MDH on facial-scratching behavior in monkeys. The MDH is located in the ventral portion of the brain stem, and is the area of first synapse of afferents with cutaneous facial receptive fields. First, dose-response curves for morphine were established. We then determined whether the effects were pharmacologically specific by administering naloxone in combination with an effective dose of morphine. We next examined the specificity of the effect of morphine within the MDH by systematically changing the site of microinjection within the MDH, and observing the areas of the face that the monkeys scratched. To determine if scratching was dependent on cutaneous histamine release, which can produce pruritus[8,9] we administered systemic chlorcyclizine, an antihistamine, in combination with MDH-administered morphine.

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Materials and Methods

Two male monkeys (*M. fascicularis*) weighing 4.5–5.5 kg were used. Monkeys received access to unlimited monkey chow, unlimited water, and some fruit. Finger mazes, balls, and music were provided to enrich the monkeys' home cage environments. These monkeys were previously trained to detect temperature changes on their face. During sessions, the monkeys sat in a Plexiglas primate-restraining chair. These chairs had two symmetrically placed L-shape holes that allowed the monkeys to reach either side of their face while restricting them from reaching the microinjection apparatus. This research met the approval of the National Institute of Dental Research Animal Care and Use Committee.

Surgical and Electrophysiologic Procedures

The first four cervical vertebrae were fused to the occipital bone, as previously described.[10] This neck fusion ensured that the monkeys could not alter the position of their necks when cannulae and microelectrodes were in the brain stem. A stainless steel chamber was implanted on the skull to support the microelectrode drive and the microinjection cannula guide.[10] After surgery, the monkeys were given 2–4 weeks to recuperate. The MDH was then systematically explored with platinum-coated tungsten microelectrodes (1–2 megaΩ at 1,000 Hz) to locate the MDH.[10–12] When neurons with response characteristics of MDH neurons were discovered, these coordinates were used for making subsequent microinjections.

Drugs

Naloxone hydrochloride and chlorcyclizine hydrochloride were purchased from Sigma Pharmaceuticals (St. Louis, MO). Morphine sulfate was purchased from Lowey Drug (Baltimore, MD). All doses are expressed as the salt form of the drugs. Drugs were dissolved in 0.9% saline, with fresh preparations being made the day of injection. Microinjections were made in a volume of 0.4 μl per injection, and intramuscular injections were made in a volume of 0.1 ml/kg.

Microinjection Apparatus

The microinjection apparatus was identical to that used by Olivéras *et al.*[11,12] Briefly, the microinjection cannula was made of 32-G stainless steel tubing. This cannula was connected to a 1-μl Hamilton syringe with polyethylene tubing. The 1-μl Hamilton syringe was driven by a Sage Instruments syringe pump (model 341b, Boston, MA). The cannula, shielded within a stainless steel guide cannula, was lowered into the brain, and extended 8–10 mm beyond the tip of the guide cannula for microinjection. The microinjection and guide cannulae were positioned with a stereotaxic positioning system.

Injection Procedures

Drugs were injected no more frequently than once every 5 days, to minimize the possibility of tolerance. Sessions were conducted in a separate quiet room. Monkeys were moved to these rooms approximately 20 min before procedures were begun or data were collected, to allow them to habituate to their surroundings. Next, the microinjection cannula was lowered to within 10 mm of the MDH. The video camera was turned on and the experimenter left the room. After 10–15 min, the experimenter returned to the room and extended the microinjection cannula out of the guide cannula and into the MDH. The syringe pump was turned on and the drugs were injected at a rate of 0.1 μl/min for 4 min. The experimenter left the room when this microinjection was completed. If a second injection was performed, the experimenter reentered the room and made this injection in the monkey's thigh. The 10–15-min period before the microinjection and the 100–120 min period after the microinjection were videotaped. When excessive scratching was observed at the end of the session, naloxone (1.0 mg/kg intramuscularly) was administered to reduce this scratching.

A dose-response curve was first obtained for morphine, with the dose order being randomly derived. Each dose and saline were administered two times, with the exception of the 5.0-μg dose of morphine in Monkey F, which was given three times. Two naloxone reversals of morphine's effects were attempted in each monkey after the dose-response curve for morphine was established. In these experiments, each monkey received a 5.0-μg microinjection of morphine, followed, after 50 min, by a systemic injection of naloxone (0.5 mg/kg intramuscularly).

The next experiment involved microinjecting morphine (5.0 μg/0.4 μl) at successively more ventral sites during two sessions for Monkey L and three sessions for Monkey F. Lastly, chlorcyclizine was administered during two sessions for each monkey. For Monkey L, chlorcyclizine was systemically injected 50 min (1.0 mg/kg intramuscularly) and 75 min (2.5 mg/kg intra-

muscularly) after a microinjection of morphine (5.0 μg). For Monkey F, chlorcyclizine was systemically injected 40 min (1.0 mg/kg intramuscularly) and 70 min (2.5 mg/kg intramuscularly) after a microinjection of morphine (5.0 μg). Naloxone (1.0 mg/kg intramuscularly) was injected 95 min after the morphine microinjection in both monkeys. For a different experiment,[13] dose-response curves for [D-Ala^2,*N*-Me-Phe^4, Gly^5-ol]enkephalin (DAMGO), [D-Pen^{2,5}]-enkephalin (DPDPE), and U50,488H were established immediately after the morphine dose-response curve was established.

Data Analysis

Statistical analysis of main effects and interactions were done with factorial ANOVA on scratches per 5 min over the entire postmicroinjection course of the sessions. Each monkey's data were individually analyzed. This is an appropriate use of population statistics such as ANOVA; however, our conclusions from these statistics need to be limited to each monkey's scratching behavior. The within degrees of freedom, presented in the results, are derived from the number of doses. The between degrees of freedom are derived from the number of 5-min periods during which data were collected. Duncan's test was used for *post hoc* analysis. An α of 0.05 or less was considered statistically significant. For all data other than the dose-response curves, only descriptive statistics were used, because there was not enough data from each monkey to allow ANOVA to be effectively used. Each videotape was scored by one or more of three raters, with the rater frequently, but not always, being unaware of the drug and dose injected for the morphine dose-response curve and naloxone reversal data. For the cannula position change manipulations and the morphine-chlorcyclizine data, two raters rated each tape, with one rater always being unaware of the drug treatment. Raters counted and recorded the number and location of facial scratches in 5-min periods. A scratch was defined as one continuous behavior in which the monkey rubbed its facial skin. Scratches were rated in terms of area (ophthalmic, maxillary, or mandibular divisions) and side of face scratched (fig. 1). If a given scratch crossed a facial area or a side of the face, a single scratch was recorded with its location being the area where the scratch was initiated. When multiple raters separately rated a single tape, responses per 5-min periods for each area were highly correlated (Pearson's $r > 0.96$), indicating high interrater reliability. Data from different raters were combined and the mean number of scratches per 5 min was used in the analysis. All data were synchronized about the microinjections.

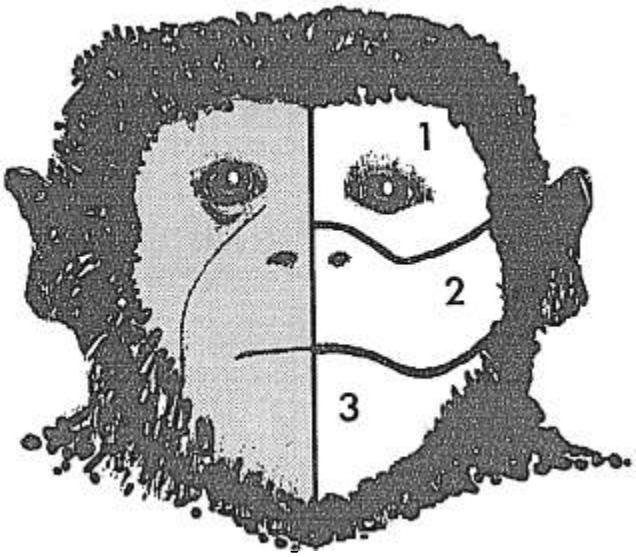

Fig. 1. Schematic representation of the areas defined as ophthalmic (1), maxillary (2), and mandibular (3) portions of the face.

Results

Morphine significantly increased scratching behavior for Monkey L ($F[4,390] = 37.3$, $P < 0.001$) and Monkey F ($F[4,447] = 32.4$, $P < 0.001$). Furthermore, both Monkey L ($F[1,390] = 38.7$, $P < 0.001$) and Monkey F ($F[1,447] = 163.0$, $P < 0.001$) scratched significantly more frequently on the side of the face that was ipsilateral to the microinjection. There was also a significant dose × side interaction for both Monkey L ($F[4,390] = 5.2$, $P < 0.001$) and Monkey F ($F[4,447] = 28.3$, $P < 0.001$). Duncan's tests were performed, comparing the effects of all doses with each other and saline. It is evident from the dose-response curves and this analysis that the higher doses of morphine produced greater increases in facial scratching (fig. 2).

The time course of morphine's effect (5.0 μg) on ipsilateral and contralateral facial scratches is presented in figure 3, in the left panels. Morphine increased scratching behavior in both monkeys within about 10–20 min of microinjection, and this scratching continued for the duration of the 2-h sessions. When the opioid antagonist naloxone (0.5 mg/kg in-

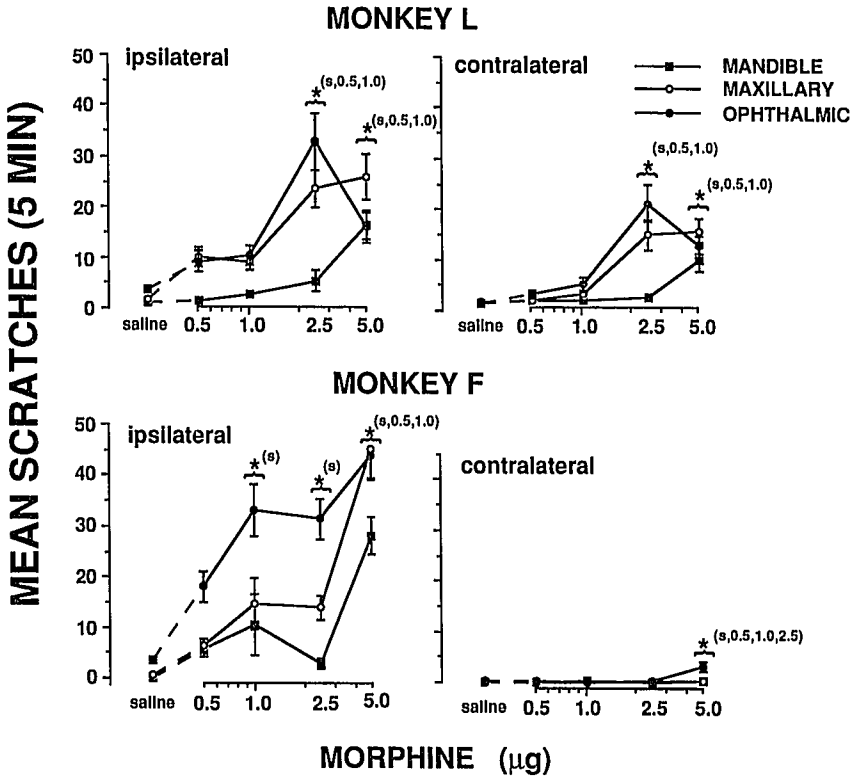

Fig. 2. Effects of morphine (0.5, 1.0, 2.5, and 5.0 μg/0.4 μl) on mean facial scratches per 5 min in areas of the face served by the ophthalmic, maxillary, and mandibular division of the trigeminal nerve. Each dose of morphine and saline was administered twice, except for the 5.0-μg dose in Monkey F, which was administered three times. Data for Monkey L (*top*) and Monkey F (*bottom*) are individually presented, as are data from the ipsilateral (*left*) and contralateral (*right*) sides of the face relative to the microinjection. Asterisks over brackets indicate that total scratches on a given side of the face (*i.e.*, ophthalmic + maxillary + mandibular areas) were significantly greater ($P < 0.05$) than the conditions indicated within the parentheses. Error bars represent ± 1 SEM, based on variability between 5-min periods.

tramuscularly) was injected 50 min after a microinjection of morphine (5.0 μg), scratching dramatically decreased (fig. 3, right panels). For both monkeys, this reversal occurred within about 5 min after naloxone administration and continued for the remainder of each session.

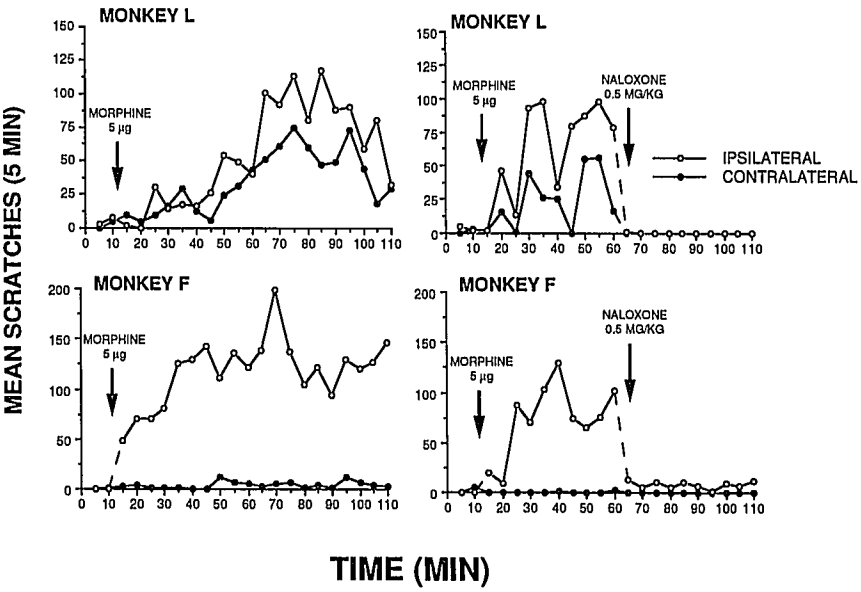

Fig. 3. (*Left*) Time course of morphine (5.0 μg/0.4 μl) on mean facial scratches per 5-min ipsilateral and contralateral to the microinjection. Data represent two sessions in each monkey. Data for Monkey L (*top*) and Monkey F (*bottom*) are individually presented. (*Right*) Effects of systemic injection of naloxone (0.5 mg/kg intramuscularly), injected 50 min after morphine (5.0 μg/0.4 μl), on mean facial scratches per 5 min ipsilateral and contralateral to the microinjection. Data represent two sessions in each monkey. Data for Monkey L (*top*) and Monkey F (*bottom*) are individually presented.

Morphine (5.0 μg/0.4 μl) was microinjected during two sessions for Monkey L and three sessions for Monkey F, at successively 1 mm more ventral sites. More ventral injection sites were associated with an increase in the percentage of scratches made in the ophthalmic region, and a reduction in scratching in the maxillary and mandibular areas (fig. 4).

The 1.0-mg dose of chlorcyclizine had little or no effect on scratching behavior. After the 2.5-mg dose of chlorcyclizine, an immediate decrease in scratching was observed for both monkeys (fig. 5). However, this decrease was short lasting. Facial-scratching behavior began to increase 10 min after the injection of chlorcyclizine in each monkey. Naloxone eliminated nearly all scratching behavior within 10 min of its injection in these experiments.

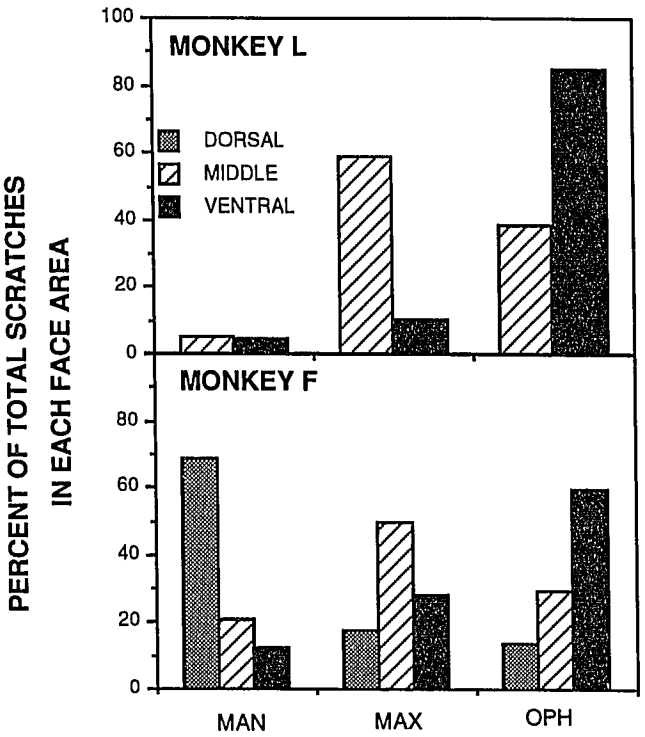

Fig. 4. Percentage of ipsilateral scratches made in the ophthalmic, maxillary, and mandibular areas of the face for Monkey L (two sessions; *top*) and Monkey F (three sessions; *bottom*) where morphine (5.0 μg/0.4 μl) was microinjected. The cannula depth was advanced ventrally between these sessions, in 1-mm units. Note that, as the cannula depth increased, modal responding shifted from the mandibular to the maxillary, and then to the ophthalmic, areas.

Discussion

Morphine microinjected into the MDH produced facial scratching ipsilateral and contralateral to the microinjection, with greater ipsilateral increases. Furthermore, with greater doses of morphine, greater increases in scratching behavior were generally found. Increases in facial-scratching behavior were seen within the same dose range of morphine previously found to produce analgesia.[11,12] Both ipsilateral and contralateral increases in facial scratching were opioid-receptor mediated, because they were reversed with naloxone administration.

Similar to our findings, morphine injected into the fourth ventricle produced scratching in a variety of species.[14] Morphine injected intrathecally has also been found to produce scratching in monkeys.[15] Olivéras *et al.*[11] demonstrated that morphine microinjected into the MDH produces facial scratching in monkeys; however, dose dependency and receptor specificity were not examined in their study. Thomas *et al.*[13] found that the μ-selective opioid-receptor agonist DAMGO, microinjected into the MDH of monkeys, produced facial-scratching behavior that was both dose dependent and naloxone reversible. DAMGO was 2–3 times more potent than was morphine in the present experiment at producing facial scratching. Scratching was not induced, in the study of Thomas *et al.*,[13] by the administration of the δ-selective opioid-receptor agonist DPDPE, nor the κ-selective opioid-receptor agonist U50,488H. Taken together with the current findings, it is clear that the MDH is a site where opioid agonists with activity at μ-opioid receptors act to produce facial-scratching behavior.

Scratching has also been produced by high doses of intrathecal opioids in rats.[16,17] However, scratching appears to be of a different origin than the scratching we observed in our paradigm and that produced by epidural and intrathecal opioids in humans. Scratching produced by high doses of intrathecal morphine in rats was not attenuated with naloxone, and 10–20 times the analgesic dose was required to produce scratching. In contrast, the facial pruritus produced by intrathecal or epidural opioids in humans was attenuated by naloxone,[3] and was observed within the analgesic dose range. Likewise, our effects of morphine were reversed by naloxone and seen within the analgesic dose range.

The contralateral increases in facial scratching were probably not the result of drug spread between areas of the brain. For drug spread to account for our findings, a significant portion of the 0.4-μl microinjections

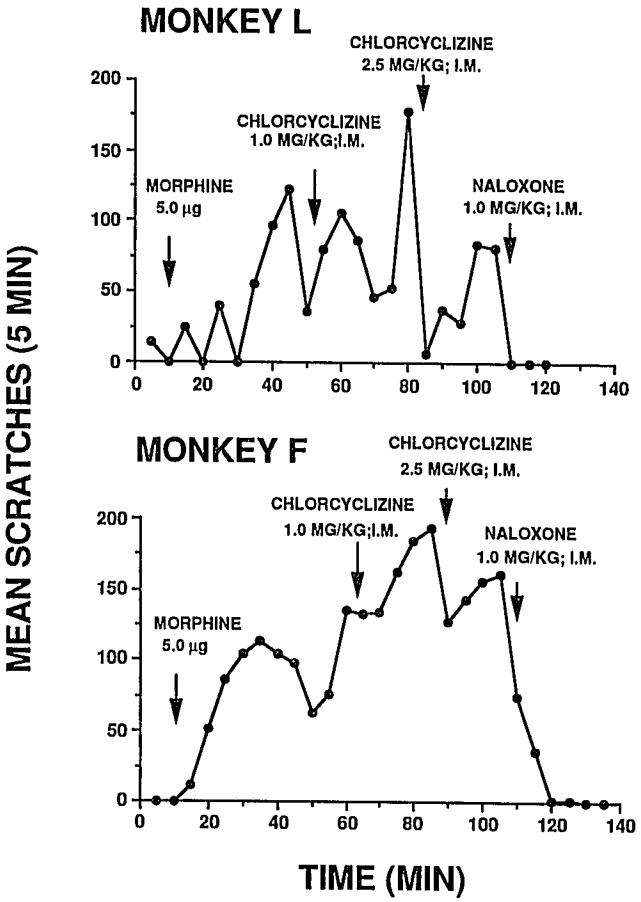

Fig. 5. (*Top*) Chlorcyclizine was systemically injected 50 min (1.0 mg/kg intramuscularly) and 75 min (2.5 mg/kg intramuscularly) after a microinjection of morphine (5.0 µg) in Monkey L. Naloxone (1.0 mg/kg intramuscularly) was injected 95 min after the morphine microinjection. Note that data are from two sessions. (*Bottom*) Chlorcyclizine was systemically injected 40 min (1.0 mg/kg intramuscularly) and 70 min (2.5 mg/kg intramuscularly) after a microinjection of morphine (5.0 µg) in Monkey F. Naloxone (1.0 mg/kg intramuscularly) was injected 95 min after the morphine microinjection. Note that data are from two sessions.

would have had to travel 3–4 mm to reach the contralateral side of the MDH within minutes of microinjection. However, when 0.5 µl of radioactively labeled morphine was microinjected into rat thalamus, 72% of the activity recovered from the brain was within 0.75 mm from the microinjection point after 30 min.[18] Furthermore, the distribution of scratching produced by 1-mm changes in cannula placement corresponded well with the somatotopic organization of the MDH.[19] The close correspondence between microinjection site and area of face scratched demonstrates a specificity of action of morphine within the MDH. Distant spread of drugs or general neural disruptions are, thus, unlikely explanations for increases in scratching, both ipsilateral and contralateral to the microinjections.

Intradermal morphine causes the release of intradermal histamine,[8] which produces pruritus.[9] Given that our microinjections were in the MDH, the first site of synapse of afferents with cutaneous facial receptive fields, morphine may have led to the release of cutaneous histamine *via* an axon reflex. However, our findings using chlorcyclizine and naloxone argue against this being the case. Chlorcyclizine produced only small, transient reductions in scratching. In contrast, chlorcyclizine was found to greatly reduce pruritus induced by intradermal histamine in humans.[20] In addition, systemically administered naloxone greatly reduced facial-scratching behavior in both monkeys. In contrast, naloxone is ineffective at reducing pruritus induced by intradermal histamine injection.[9,21] (However, see reference 22.)

Ballantyne *et al.*[1] hypothesized that spinal opioids produce facial pruritus by reaching the medulla and activating opioid receptors. This is supported by the fact that the medulla is rich in opioid receptors and is readily exposed to CSF ascending from the spinal cord. Alternatively, Scott and Fischer[23] have hypothesized that spinal opioids produce a change in neural activity at the level of the injection, resulting in altered neural activity at the brain stem level and, ultimately, facial pruritus.[23] Clearly, we have shown that morphine at the level of the brain stem is sufficient to produce opioid-receptor-mediated scratching. However, we also found contralateral facial scratching, which was probably the result of neural mechanisms, perhaps like those described by Scott and Fischer.[23]

Support for the neural hypothesis comes from studies of CSF flow, in which it was demonstrated that spinal radioactively labeled drugs do not reach the brain stem in time to account for facial pruritus.[24,25] However, it has also been shown that, after epidural injection of morphine or sufentanil, there is a rapid appearance of these agents in the cisterna magna,[26,27] which may result from vascular redistribution. Likewise, CSF flow can radically increase under conditions of strain[28] (*e.g.*, coughing, sneezing, etc.). Strain may increase the probability of epidural or intrathecal opioids reaching the brain stem and producing pruritus. Accordingly, the clinical situation in which opioids very frequently produce facial pruritus is during childbirth,[29–31] a condition of considerable strain. A systematic study examining strain, blood flow, and incidence of pruritus

after spinal opioid administration would help to resolve some of the unanswered questions in this area.

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