

# Production of Paradoxical Sensory Hypersensitivity by $\alpha_2$ -Adrenoreceptor Agonists

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**Background:** Administration of opioid receptor agonists is followed by paradoxical sensory hypersensitivity. This hypersensitivity has been suggested to contribute to the antinociceptive tolerance observed with opioids. The authors hypothesized that  $\alpha_2$ -adrenoreceptor agonists, which also produce antinociceptive tolerance, would produce sensory hypersensitivity.

**Methods:**  $\alpha_2$ -Adrenoreceptor agonists were administered to male Sprague-Dawley rats as a single subcutaneous injection, a continuous subcutaneous infusion, a single intrathecal injection, or a continuous intrathecal infusion. Thermal sensitivity was determined using latency to withdrawal of the hind paw from radiant heat. Tactile sensitivity was determined using withdrawal threshold to von Frey filaments. Spinal dynorphin content was measured by enzyme immunoassay.

**Results:** Single systemic or intrathecal injections of clonidine or dexmedetomidine produced antinociception followed by delayed thermal and tactile hypersensitivity. Six-day systemic or intrathecal infusion of clonidine produced tactile and thermal hypersensitivity observed even during clonidine infusion. Sensory hypersensitivity was prevented by coadministration of the  $\alpha_2$ -adrenoreceptor-selective antagonist idazoxan or the *N*-methyl-D-aspartate receptor-selective antagonist MK-801. Six-day infusion of intrathecal clonidine increased dynorphin content in dorsal lumbar spinal cord. MK-801 and dynorphin antiserum reversed clonidine-induced sensory hypersensitivity.

**Conclusions:**  $\alpha_2$ -Adrenoreceptor agonists produce sensory hypersensitivity that may be analogous to that produced by opioids. Sensory hypersensitivity was prevented by idazoxan, demonstrating that it is mediated by  $\alpha_2$  receptors. Clonidine infusion increased spinal dynorphin content. Sensory hypersensitivity was prevented or reversed by MK-801 and dynorphin antiserum, implicating *N*-methyl-D-aspartate receptors and spinal dynorphin in its production. Clinicians should be mindful of the possibility of drug-induced hyperalgesia in patients treated with  $\alpha_2$ -adrenoreceptor agonists.

$\alpha_2$ -ADRENORECEPTOR-selective agonists are administered both acutely and chronically for a variety of indications.<sup>1,2</sup> Many of the acute uses of  $\alpha_2$ -receptor agonists occur at the time of surgery.<sup>2</sup> They decrease the amount of general anesthetic agents required, provide sedation, decrease hemodynamic fluctuations caused by anes-

sia and surgery, prevent postoperative shivering, and may decrease perioperative myocardial ischemia. In addition, because of their analgesic properties, they may improve postoperative pain control and decrease the amount of other analgesic agents (e.g., opioids) needed.

The  $\alpha_2$ -receptor agonist clonidine is also administered systemically or perispinally for the treatment of chronic pain.<sup>1</sup> Although epidural administration for the treatment of cancer pain is the only pain application approved by the US Food and Drug Administration, clonidine has been administered orally, transdermally, and intrathecally for the treatment of pain syndromes of both malignant and benign causes. Clonidine has also been used chronically for the treatment of hypertension, congestive heart failure, and ischemic heart disease.

We hypothesized that  $\alpha_2$ -receptor agonists would produce sensory hypersensitivity based on comparison with  $\mu$ -opioid receptor systems. Prolonged or repeated administration of  $\alpha_2$ -receptor agonists results in antinociceptive tolerance.<sup>3–5</sup> Antinociceptive tolerance to opioids has been hypothesized to result from a decrease in nociceptive threshold, leading to an increase in the dose of drug required to overcome this increased pain sensitivity.<sup>6,7</sup> Therefore, we hypothesized that  $\alpha_2$ -adrenoreceptor agonists might also produce a paradoxical decrease in nociceptive thresholds. This work was also performed in light of the observation by Takano and Yaksh<sup>4</sup> that continuous intrathecal infusion of  $\alpha_2$ -receptor agonists produced touch-evoked allodynia.

## Materials and Methods

### Animals

Approval was obtained from the University of Arizona Animal Care and Use Committee (Tucson, Arizona). Male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) weighed 200–300 g at the time of testing. They were allowed food and water *ad libitum* and were maintained in a climate-controlled room on a 12-h light/dark cycle. All animal procedures conformed to the guidelines of the National Institutes of Health and the International Association for the Study of Pain.

### Intrathecal Catheter Implantation

Rats were chronically implanted with intrathecal catheters as described by Yaksh and Rudy.<sup>8</sup> Rats were anesthetized with halothane and placed in a stereotactic head holder. The occipital muscles were separated from their insertion on the skull and retracted caudally to expose

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the cisternal membrane. The membrane was incised, and polyethylene tubing was passed caudally from the cisterna magna to the level of the lumbar enlargement. Animals with evidence of neurologic deficits (< 1%) were promptly euthanized. Intrathecal drug administration was performed by delivering the drug in a volume of 5  $\mu$ l, followed by a 9- $\mu$ l saline flush.

#### *Prolonged Infusion Using Osmotic Minipumps*

Prolonged infusions were performed using osmotic minipumps (model 2001; Alza, Mountain View, CA). For subcutaneous infusion, a small incision was made in the skin between the scapulae. A small pocket was formed in the subcutaneous connective tissue, and the minipumps were placed in the pocket, with the flow moderator pointing away from the incision. For spinal infusions, minipumps were attached to the indwelling intrathecal catheters and placed in subcutaneous pockets. Skin incisions were sutured closed. For intrathecal bolus injection of drugs after intrathecal clonidine infusion, animals were anesthetized with halothane, the intrathecal catheter was exteriorized, the minipump was disconnected, and drugs were injected through the catheter in a volume of 5  $\mu$ l followed by a 9- $\mu$ l saline flush.

#### *Drugs*

Clonidine was obtained from Tocris (Ellisville, MO). Idazoxan hydrochloride and (+)-MK-801 were obtained from Sigma (St. Louis, MO). Antiserum to dynorphin A (1-17) was obtained from Bachem/Peninsula Laboratories (San Carlos, CA). This rabbit antiserum was 100% cross-reactive with dynorphin (1-13) and dynorphin (1-8).

#### *Assessment of Mechanical Sensitivity*

Rats were allowed to acclimate for 30 min within Plexiglas® enclosures with wire mesh bottoms. Paw withdrawal thresholds were determined in response to probing of the hind paw with a series of calibrated von Frey filaments applied perpendicularly to the plantar surface of the paw. A maximal cutoff of 15 g was used because larger filaments lifted the paw even if the animal did not actively withdraw. Data were analyzed by the up-and-down method of Dixon, as described by Chaplan *et al.*<sup>9</sup>

#### *Assessment of Thermal Sensitivity*

Thermal sensitivity was assessed as described by Hargreaves *et al.*<sup>10</sup> Rats were allowed to acclimate within Plexiglas® enclosures on a clear glass plate maintained at 30°C. A radiant heat source was focused onto the plantar surface of the hind paw. The stimulus and the timer were both interrupted when withdrawal of the hind paw was detected by a photodetection device. A maximal cutoff of 40 s was used to prevent tissue damage.

#### *Dynorphin Immunoassay*

Rats were deeply anesthetized with ether and decapitated. Transverse incisions were made into the upper

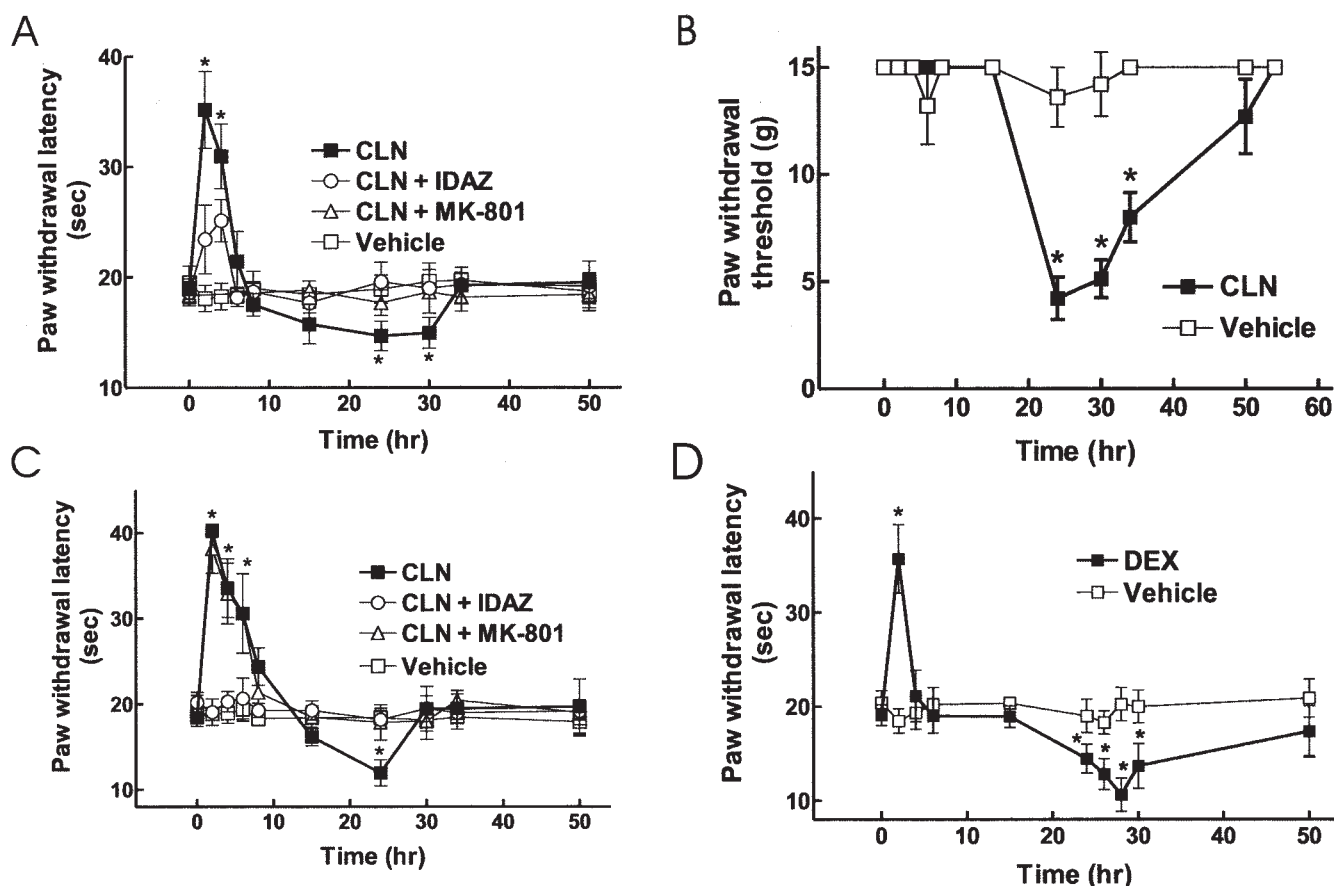
cervical and the sacral spinal column. The spinal cord was ejected using ice-cold saline and placed on a glass Petri dish that was resting on ice. The lumbar spinal cord was rapidly dissected, and the dorsal spinal cord was dissected from the ventral spinal cord at the level of the central canal. Tissue samples of dorsal spinal cord were rapidly frozen on dry ice and stored at -70°C. For immunoassay, thawed tissue was placed in 1 N acetic acid, disrupted with a Polytron homogenizer (Polytron Corp., Elkhart, IN), and incubated for 20 min at 95°C. After centrifugation at 10,000g for 20 min (4°C), the supernatant was lyophilized and stored at -70°C. The lyophilized supernatant was dissolved in water, and protein concentrations were determined using the bicinchoninic acid method with bovine serum albumin as a standard. Immunoassay was performed using a commercial immunoassay kit with an antibody specific for dynorphin A (1-17) (Bachem/Peninsula Laboratories).

#### *Statistical Analysis*

The assessment of time effects of drugs and individual group comparisons were performed using one-way and two-way analyses of variance. *Post hoc* analyses were performed using the Dunnett test when posttreatment values were compared with baseline values and using the Student *t* test when different treatment groups were compared. When only two treatment groups were compared, the Student *t* test was used. Differences with *P* < 0.05 were considered significant.

## **Results**

A single systemic injection of the  $\alpha_2$ -adrenoreceptor-selective agonist clonidine (1.2 mg/kg subcutaneous) resulted in transient antinociception to a thermal stimulus followed by delayed thermal hypersensitivity 24–30 h after clonidine injection (fig. 1A). Both the antinociception and the thermal hypersensitivity were prevented by coadministration of the  $\alpha_2$ -adrenoreceptor-selective antagonist idazoxan (3 mg/kg subcutaneous, 10 min before clonidine and every 2 h for three doses). MK-801 (0.15 mg/kg subcutaneous, 10 min before clonidine) prevented clonidine-induced thermal hypersensitivity. The effects of MK-801 on the antinociceptive phase were not tested because of concerns regarding centrally mediated behavioral effects of MK-801 in the first few hours after systemic administration. Similarly, a single subcutaneous injection of clonidine (1.2 mg/kg) resulted in delayed tactile hypersensitivity 24–34 h after clonidine administration (fig. 1B). A single subcutaneous injection of clonidine resulted in tactile and thermal hypersensitivity 24 h after clonidine administration if sensory testing was not performed in the intervening time period, demonstrating that the observed sensory hypersensitivity was not due to repeated sensory testing



**Fig. 1.** A single dose of  $\alpha_2$ -adrenoreceptor-selective agonist produces antinociception followed by sensory hypersensitivity. (A) Antinociception and thermal hypersensitivity produced by systemic (subcutaneous) clonidine (CLN). (B) Tactile hypersensitivity produced by systemic subcutaneous clonidine. (C) Antinociception and thermal hypersensitivity produced by spinal (intrathecal) clonidine. (D) Antinociception and thermal hypersensitivity produced by intrathecal dexmedetomidine (DEX). Where tested, the  $\alpha_2$ -adrenoreceptor-selective antagonist idazoxan (IDAZ) prevented the production of antinociception and thermal hypersensitivity. Where tested, the *N*-methyl-D-aspartate receptor antagonist MK-801 prevented the production of thermal hypersensitivity. Data are expressed as mean  $\pm$  SEM;  $n = 6$  per group. \*  $P < 0.05$  compared with vehicle control.

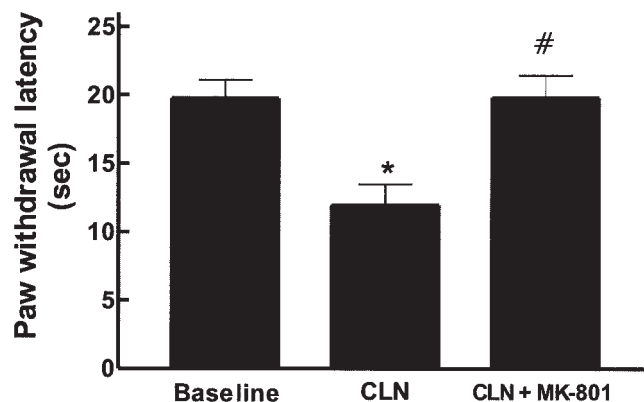
(thermal withdrawal latency 24 h after vehicle [saline] injection =  $21.5 \pm 0.4$  s [mean  $\pm$  SEM], withdrawal latency 24 h after clonidine injection =  $16 \pm 1$  s [ $P < 0.05$ ]; tactile withdrawal threshold 24 h after vehicle [saline] injection =  $13 \pm 1$  g, withdrawal threshold 24 h after clonidine injection =  $2.9 \pm 0.7$  g [ $P < 0.05$ ]).

A single intrathecal injection of clonidine (300  $\mu$ g) resulted in transient antinociception to a thermal stimulus, followed by delayed thermal hypersensitivity 24 h after clonidine injection (fig. 1C). These effects were prevented by coadministration of idazoxan (150  $\mu$ g intrathecal, 10 min before clonidine). MK-801 (3.4  $\mu$ g intrathecal, 10 min before clonidine) did not affect the antinociceptive phase but did prevent the thermal hypersensitivity. Similarly, a single intrathecal injection of the  $\alpha_2$ -adrenoreceptor-selective agonist dexmedetomidine (30  $\mu$ g) resulted in transient antinociception to a thermal stimulus, followed by delayed thermal hypersensitivity 26–28 h after dexmedetomidine injection (fig. 1D).

Intrathecal MK-801 (3.4  $\mu$ g) reversed the thermal hy-

persensitivity produced by a single dose of intrathecal clonidine (300  $\mu$ g) when administered 24 h later (fig. 2).

Continuous systemic infusion of clonidine (10  $\mu$ g/h



**Fig. 2.** Intrathecal MK-801 reverses the thermal hypersensitivity produced by a single dose of intrathecal clonidine (CLN). MK-801 was administered 24 h after clonidine. Data are expressed as mean  $\pm$  SEM;  $n = 6$  per group. \*  $P < 0.05$  compared with vehicle control. #  $P < 0.05$  compared with clonidine alone.

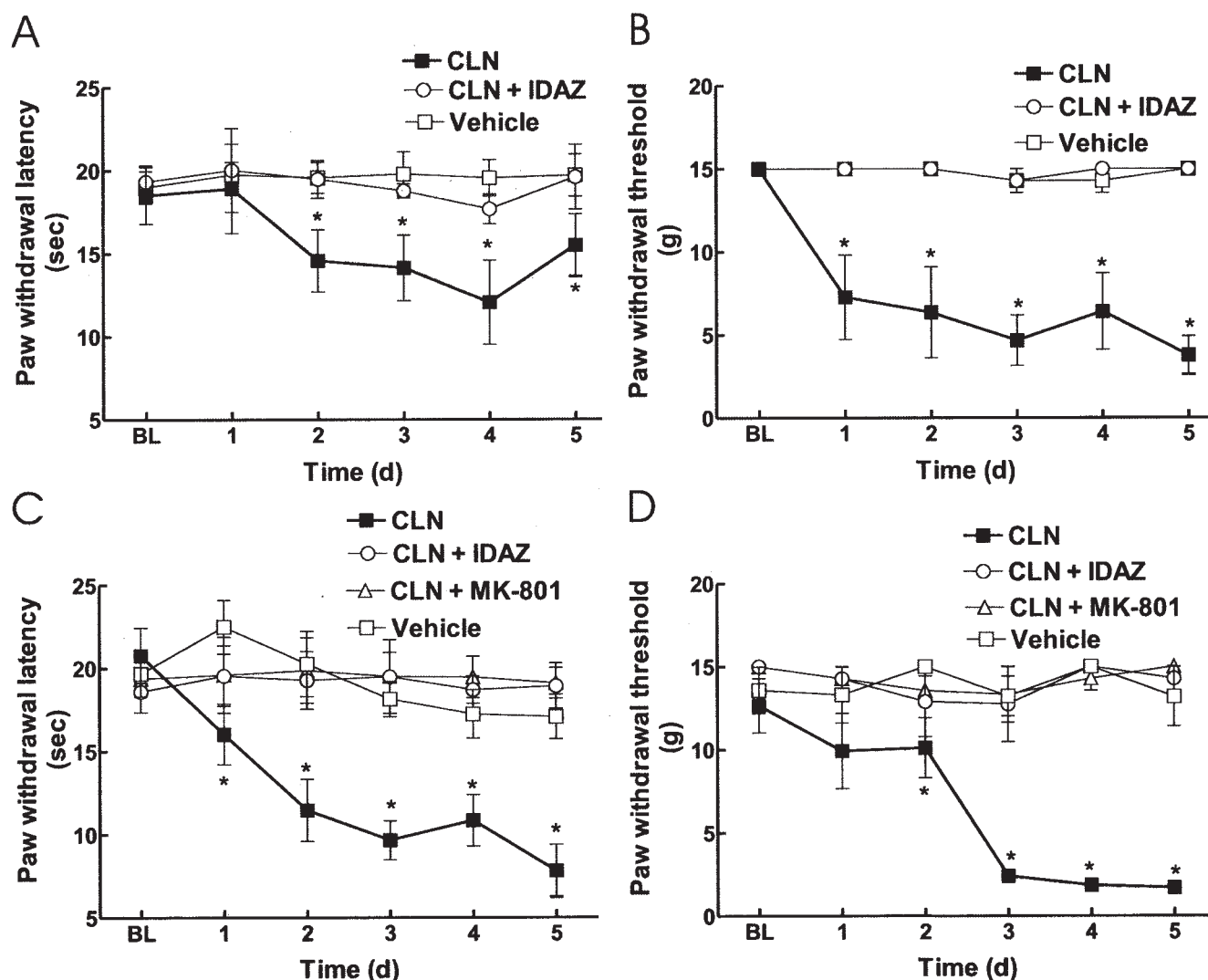


Fig. 3. Prolonged (5-day) infusions of clonidine (CLN) produce sensory hypersensitivity. (A) Production of thermal hypersensitivity by subcutaneous clonidine. (B) Production of tactile hypersensitivity by subcutaneous clonidine. (C) Production of thermal hypersensitivity by intrathecal clonidine. (D) Production of tactile hypersensitivity by intrathecal clonidine. Coinfusion of the  $\alpha_2$ -adrenoreceptor-selective antagonist idazoxan (IDAZ) prevented the production of thermal and tactile hypersensitivity. Where tested, the *N*-methyl-D-aspartate receptor antagonist MK-801 prevented the production of sensory hypersensitivity. Data are expressed as mean  $\pm$  SEM;  $n = 6$  per group. \*  $P < 0.05$  compared with vehicle control.

subcutaneous) resulted in thermal hypersensitivity 2 days after initiation of the infusion (fig. 3A) and tactile hypersensitivity 1 day after initiation of the infusion (fig. 3B). This sensory hypersensitivity was completely prevented by coinfusion of idazoxan (200  $\mu$ g/h subcutaneous) using a second minipump.

Continuous intrathecal infusion of clonidine (30 nm/h) resulted in thermal hypersensitivity 1 day after initiation of the infusion (fig. 3C) and tactile hypersensitivity 2 days after initiation of infusion (fig. 3D). This sensory hypersensitivity was completely prevented by coinfusion of idazoxan (200  $\mu$ g/h intrathecal) or MK-801 (0.7  $\mu$ g/h intrathecal) through a second minipump and intrathecal catheter.

After 5 days of intrathecal clonidine infusion, content of dynorphin A (1-17) in dorsal lumbar spinal cord was

increased twofold compared with vehicle (saline)-treated animals (fig. 4).

Intrathecal MK-801 (3.4  $\mu$ g) or intrathecal dynorphin antiserum (200  $\mu$ g) administered after 5 days of clonidine infusion reversed the thermal and tactile hypersensitivity produced by continuous infusion of intrathecal clonidine (30 nm/h) (fig. 5).

## Discussion

$\alpha_2$ -Adrenoreceptor-selective agonists produce paradoxical sensory hypersensitivity. Acute administration of  $\alpha_2$  agonists results in antinociception to thermal stimuli followed by delayed sensory hypersensitivity. These results suggest that  $\alpha_2$ -adrenoreceptor-selective agonists



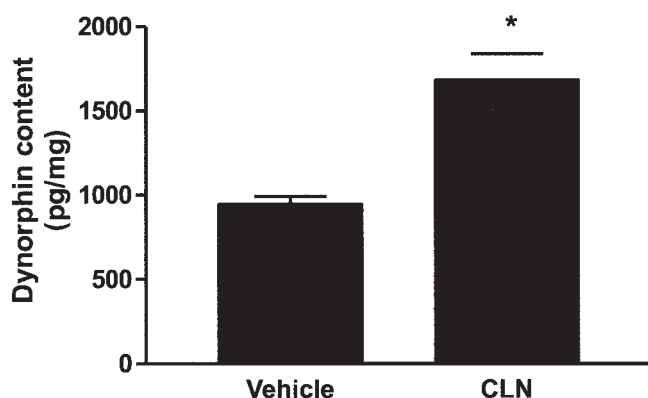


Fig. 4. Intrathecal clonidine (CLN) infusion increases dynorphin content in dorsal spinal cord. Spinal dynorphin content was measured after 5 days of clonidine infusion. Data are expressed as mean  $\pm$  SEM;  $n = 6$  per group. \* $P < 0.05$  compared with vehicle control.

activate not only antinociceptive systems, but also pronociceptive systems with longer activity. Continuous administration of  $\alpha_2$  agonists produces sensory hypersensitivity that is observed even during  $\alpha_2$ -agonist infusion, showing that this sensory hypersensitivity is not the result of a drug withdrawal syndrome.

Clonidine-induced sensory hypersensitivity is prevented by coadministration of the  $\alpha_2$ -adrenoreceptor-selective antagonist idazoxan, demonstrating that it is mediated by  $\alpha_2$  adrenoreceptors. Dexmedetomidine, a more selective  $\alpha_2$ -adrenoreceptor agonist, also produced thermal hypersensitivity after intrathecal administration, providing further support for the concept that activation of  $\alpha_2$  receptors is sufficient to produce delayed sensory hypersensitivity.

These experiments used high doses of  $\alpha_2$ -receptor-selective agonists. Typically, these were selected from published articles as the highest doses that were used to study antinociception or drug tolerance. This was done to maximize the likelihood of detecting  $\alpha_2$ -agonist-induced sensory hypersensitivity. This raises the question of whether similar effects would be observed at the doses of  $\alpha_2$ -receptor-selective agonists that are used for pain relief in humans. This issue is difficult to address directly in animals because of species differences in drug

potency. However, in preliminary experiments, doses much smaller than those used here (for example, a clonidine infusion of 0.03 nmol/h) seem to result in sensory hypersensitivity (unpublished data, January 2004, M. Higashi, M.D., and T. P. Malan, Jr., Ph.D., M.D., Tucson, Arizona). The use of high doses of clonidine also raises the question of whether some of the effects seen may have been due to cross-reactivity at  $\alpha_1$  adrenoreceptors. However, this is unlikely because the effects of clonidine were completely prevented by idazoxan, an  $\alpha_2$ -receptor-selective antagonist.

Qualitatively, these effects seem similar to the paradoxical increase in pain sensitivity produced by opioid receptor agonists. Acute administration of opioid receptor agonists produces delayed sensory hypersensitivity after resolution of opioid antinociceptive effects. Laulin *et al.*<sup>11</sup> showed that a single subcutaneous injection of heroin resulted in an antinociceptive phase followed by a decreased response threshold to mechanical stimuli. Similar results were obtained using four injections of fentanyl at 15-min intervals.<sup>12</sup> Sensory hypersensitivity is also observed during prolonged opioid administration. Repeated morphine or heroin administration results in sensory hypersensitivity.<sup>6,13</sup> Importantly, sustained opioid administration also results in tactile and thermal hypersensitivity, indicating that this hypersensitivity is not due to intermittent drug withdrawal.<sup>14-16</sup>

The duration of the sensory hypersensitivity produced by acute administration of  $\alpha_2$ -adrenoreceptor agonists (a few hours) was significantly less than the reported duration of the sensory hypersensitivity produced by acute administration of opioids (days).<sup>12,17</sup> It is not clear whether this difference in duration reflects significant differences in the effects of the two drug classes, differences in the relative doses of drugs used, or other differences in experimental methods. The magnitude of sensory hypersensitivity after acute bolus administration of clonidine cannot be compared to the magnitude of the sensory hypersensitivity produced by acute administration of opioids in published studies,<sup>12,17</sup> because different measures of sensory sensitivity were used. However, the magnitude of sensory hypersensitivity produced by a 5-day

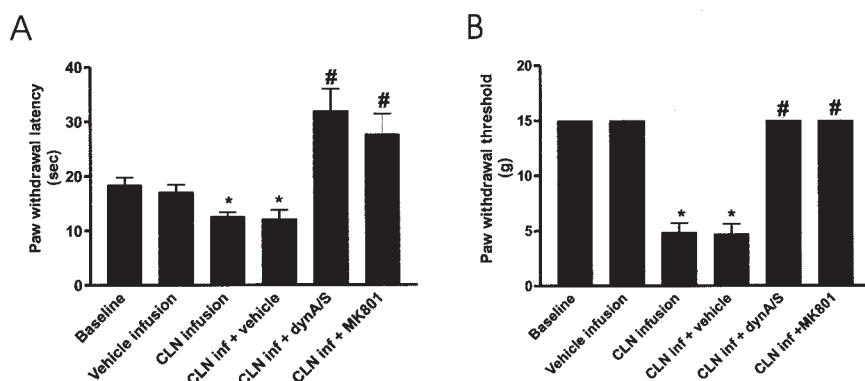


Fig. 5. Intrathecal MK-801 or dynorphin antiserum (dynA/S) reverse the thermal (A) and tactile (B) hypersensitivity produced by a prolonged (5-day) infusion of intrathecal clonidine (CLN). Drugs were administered after 5 days of clonidine infusion. Data are expressed as mean  $\pm$  SEM;  $n = 6$  per group. \* $P < 0.05$  compared with vehicle control. # $P < 0.05$  compared with clonidine alone.

infusion of clonidine in our studies is similar to the magnitude of sensory hypersensitivity produced by prolonged administration of opioids in published work in which identical sensory testing methods were used.<sup>14</sup>

Dynorphin content in the dorsal spinal cord is increased after a 5-day intrathecal infusion of clonidine, and clonidine-induced sensory hypersensitivity is inhibited by sequestration of dynorphin using intrathecal administration of an antiserum to dynorphin, suggesting that actions of spinal dynorphin are required for clonidine-induced sensory hypersensitivity. In addition, clonidine-induced sensory hypersensitivity is inhibited by *N*-methyl-D-aspartate receptor antagonists. Interestingly, when administered during sustained intrathecal clonidine infusion, dynorphin antiserum and MK-801 prolong thermal withdrawal latency beyond preinfusion baseline values, perhaps by unmasking the antinociceptive effects of clonidine. These findings are identical to observations in studies of opioid-induced sensory hypersensitivity,<sup>12-14,18,19</sup> suggesting that the same mechanisms may be responsible for both phenomena. Opioid-induced sensory hypersensitivity seems to be mediated by *N*-methyl-D-aspartate receptors and by actions of protein kinase C.<sup>12,13,18,19</sup> It may also be mediated by systems-level mechanisms. Published data suggest that sustained morphine administration activates descending facilitation from the rostral ventromedial medulla,<sup>15</sup> leading to an increase in spinal dynorphin expression,<sup>14,20</sup> which in turn leads to increased excitatory neurotransmitter release from the spinal terminals of primary afferent fibers,<sup>21</sup> and the facilitation of spinal transmission of pain signals.

When administered acutely, opioid receptor agonists have been reported to increase pain sensitivity in healthy volunteers<sup>22</sup> and to increase postoperative pain and opioid requirements in surgical patients,<sup>23,24</sup> although contrasting results have also been reported.<sup>25</sup> In addition, high-dose long-term perispinal morphine administration was associated with paradoxical hyperalgesia, allodynia, or both in a review of 750 patients,<sup>26</sup> and case reports have described new pains differing in character or location from the pain precipitating treatment in patients receiving perispinal opioids.<sup>27-29</sup> Finally, increased sensory sensitivity has also been noted in patients with opioid addiction who were receiving long-term opioid maintenance therapy.<sup>30,31</sup>

In contrast, paradoxical pain has not been reported in patients being treated systemically or perispinally with  $\alpha_2$ -adrenoreceptor agonists. There are several reasons why such pain may not have been reported, even if it exists. First,  $\alpha_2$ -receptor agonist-induced sensory hypersensitivity has not been systematically tested in patients. Second, fewer patients have received intrathecal clonidine than have received intrathecal morphine, making the spontaneous detection of a rare event less likely. Third, intrathecal clonidine is often administered in com-

bination with intrathecal opioids. Because opioid-induced paradoxical pain is well recognized, any  $\alpha_2$ -receptor agonist-induced hyperalgesia may have been attributed by the treating physician to the spinal opioid and not reported. Finally, because until now there have been no preclinical data describing the production of paradoxical pain by  $\alpha_2$ -adrenoreceptor agonists, clinicians may not have been looking for it in their patients. Large doses of intrathecal morphine have been known since 1981 to produce a paradoxical increase in sensory sensitivity in animals.<sup>32</sup>

In conclusion, physicians should be mindful of the possibility that  $\alpha_2$ -adrenoreceptor agonists might produce paradoxical pain in the same way that administration of opioid receptor agonists sometimes does. The clinical correlate of an increase in thermal sensitivity is not clear; however, tactile hypersensitivity (tactile allodynia) has been noted in patients with opioid-induced hyperalgesia. An  $\alpha_2$ -adrenoreceptor agonist-induced increase in pain sensitivity might worsen existing pains, cause new pains, or interfere with the analgesic effectiveness of  $\alpha_2$ -receptor agonists or other drugs used for pain treatment. These considerations might suggest that we should stop using  $\alpha_2$ -adrenoreceptor agonists for pain therapy. However, it would be unfortunate to prematurely discontinue this use of  $\alpha_2$  agonists, because our options for treating pain are limited and because opioid receptor agonists, the most important drugs used for the treatment of moderate-to-severe pain, produce a similar paradoxical increase in sensory hypersensitivity. A more prudent approach would be to develop ways of reversing analgesic drug-induced sensory hypersensitivity, such as combining these drugs with *N*-methyl-D-aspartate receptor antagonists or with novel drugs that inhibit other steps in the pathways leading to sensory hypersensitivity. Therefore, it is important that we understand the potential for these drugs to produce paradoxical pain, study the mechanisms behind such pains, and develop means to limit the production of  $\alpha_2$ -receptor agonist-induced paradoxical pain.

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