Alpha₂-adrenergic receptor subtype specificity of intrathecally administered tizanidine used for analgesia for neuropathic pain

JAMES W. LEIPHART, M.D., PH.D., CYNTHIA V. DILLS, B.S., AND ROBERT M. LEVY, M.D., PH.D.

Division of Neurosurgery, University of California, Los Angeles, California; and Departments of Neurosurgery and Physiology, and Institute for Neuroscience, Northwestern University, Chicago, Illinois

Object. Intrathecally administered α₂-adrenergic receptor subtype–specific antagonists were used to determine which α₂-adrenergic receptor subtype mediates the analgesic effect of intrathecally administered tizanidine in a chronic constriction injury (CCI) rat model of neuropathic pain.

Methods. Seven days after CCI and intrathecal catheter surgeries had been performed in Sprague–Dawley rats, baseline neuropathic pain tests including cold-floor ambulation and paw pinch were performed. Either the dimethyl sulfoxide vehicle (seven rats) or one of the antagonists—5, 23, or 46 μg yohimbine (22 rats); 5, 25, 50, or 100 μg prazosin (25 rats); or 5, 45, or 90 μg WB4101 (11 rats)—were intrathecally administered to the animals, followed in 30 minutes by 50 μg intrathecally administered tizanidine. The neuropathic pain tests were repeated 30 minutes later. The resulting profile showed a descending order of antagonist efficacy for yohimbine, prazosin, and WB4101 for the cold-floor ambulation test and for the paw-pinch test of the affected paw. As expected given tizanidine’s lack of analgesic effect on the contralateral, normal paw, there were no effects of antagonists on contralateral paw responses. The results of the paw-pinch test on the affected side were compared with binding data cited in the existing literature for the three different α₂-adrenergic receptor subtypes (α₂A, α₂B, and α₂C) with yohimbine, prazosin, and WB4101. The antagonist response profile for the paw-pinch test of the affected paw most closely approximated the α₂A receptor binding profile.

Conclusions. The antagonist profile from the current study is most consistent with the theory that the α₂A-adrenergic receptor subtype mediates the analgesic effect of intrathecally administered tizanidine on CCI-associated neuropathic pain.

Key Words • neuropathic pain • intrathecal drug infusion • alpha₂-adrenergic receptor • receptor subtype • analgesia • tizanidine • rat

Various intrathecally administered drugs have proved to be analgesic in the CCI rat model of neuropathic pain, including N-methyl-D-aspartate antagonists, opiates, and α₂-adrenergic agonists. Intrathecally administered tizanidine, an α₂-adrenergic agonist, has been shown to produce antinociception and analgesia and to be well tolerated during long-term administration in animals. Human trials of intrathecally administered tizanidine for the treatment of pain have been proposed, emphasizing the importance of studying the underlying pharmacology of the analgesic effect. The analgesia produced by intrathecally administered tizanidine has demonstrated specificity for neuropathic pain signs, leaving acute nociception relatively unaffected. Intrathecally administered ST-91, another α₂-adrenergic agonist, has proved to be analgesic bilaterally at low doses in rats with CCI but more analgesic in the contralateral paw than in the affected paw at high doses. The different α₂-adrenergic subtype specificities of these two drugs may possibly underlie the difference in their observed analgesic effects.

The α₂-adrenergic receptor has been pharmacologically classified into three subtypes: α₂A, α₂B, and α₂C. In the spinal cord the predominant receptor subtype is α₂A, which is located primarily in the superficial lamina. The α₂A-adrenergic receptor has also been found in the spinal cord, but in a lower concentration than the α₂A-adrenergic receptor, and it is located diffusely throughout all lamina. The α₂B-adrenergic receptor is not present in physiological concentrations in the spinal cord, but has been found in dorsal root ganglia along with the α₂A-adrenergic receptor.

Little research has been conducted to determine which one of the three subtypes of the α₂-adrenergic receptor primarily mediates α₂-adrenergic agonist–induced analgesia in the spine. When intrathecally administered, clonidine, ST-91, and dexmedetomidine, all α₂-adrenergic agonists, have induced analgesia in healthy rats undergoing the hot-plate test. Using the subtype-specific antagonists prazosin, WB4101, and imiloxan, it was determined that ST-91–induced analgesia was mediated by a non-A subtype of the α₂-adrenergic receptor, and that dexmedetomidine–induced...
analgesia was mediated by the \( \alpha_2 \) subtype.\(^{41,44} \) Clonidine appears to act through the same receptor subtype as both ST-91 and dexametadomidine,\(^{48} \) and there is evidence of mostly an \( \alpha_2 \) subtype activity.\(^{12,21,42–44} \) In rats with experimentally induced neuropathic pain, intrathecally administered ST-91\(^{16} \) has induced less analgesia for neuropathic pain signs than for acute nociceptive pain signs, whereas tizanidine has produced greater analgesia for neuropathic pain signs than for acute nociceptive pain signs.\(^{19} \) There is evidence that the \( \alpha_2 \)-adrenergic receptor subtype may mediate tizanidine’s spinal analgesic effect.\(^{34} \)

In this study, we attempted to determine the subtype of the \( \alpha_2 \)-adrenergic receptor that primarily mediates the analgesia produced by intrathecally administered tizanidine in rats with neuropathic pain. To this end, we used the \( \alpha_2 \)-adrenergic antagonist prazosin, which is also an \( \alpha_2 \) subtype–specific antagonist at high concentrations,\(^{8} \) and the \( \alpha_2 \)-adrenergic antagonist WB4101, which is also an \( \alpha_2 \), \( \alpha_3 \) subtype–specific antagonist at high concentrations.\(^{28,29} \) We compared the effects of prazosin and WB4101 with the effect of tizanidine on cold-related allodynia. The rats were placed on a 0.13-in-thick aluminum surface on which they were standing as a correlate measure of their symptomatic animals raised their affected hind limbs from the chilled surface on which they were standing as a correlate measure of their cold-related allodynia. The rats were placed on a 0.13-in-thick aluminum floor, which had been chilled to \(-4^\circ\) C by an underlying freezer. This temperature does not evoke pain-related responses from healthy rats. An event recorder was used to measure the frequency

**Materials and Methods**

The experimental protocol for this study was reviewed and approved by the Animal Care and Use Committee of Northwestern University. Given the complex nature and relative lack of understanding of the mechanisms of neuropathic pain, no adequate alternative to an animal model currently exists to study this debilitating disease process. Every effort was taken to minimize the number of animals that were used to complete this experiment by restricting the number of experimental groups to the minimum number necessary to draw conclusions from the data.

One hundred seventeen male Sprague–Dawley rats (weighing 250–300 g each) were used in the experiment. The chronic neuropathic pain model used in this study was originally described by Bennett and Xie.\(^4 \) The rats were given 1 mg/kg atropine subcutaneously and anesthetized with 55 mg/kg sodium pentobarbital administered intraperitoneally. The common sciatic nerve was exposed at the level of the middle thigh by blunt dissection through the biceps femoris muscle. Four loose ligatures of 4-0 chromic gut suture were tied around the nerve at 1-mm intervals. The ligatures were tied to constrict just the surface of the nerve as seen under magnification \((\times 40)\). The incision was then closed with 4-0 nylon interrupted vertical mattress sutures. The rats were positioned in a stereotactic apparatus for implantation of the intrathecal catheter. Spinal catheterization was performed following the protocol of Yaksh and Rudy.\(^{30} \) The posterior portion of the head and upper cervical region of the rats were shaved and prepared with betadine solution. Using a No. 11 blade scalpel, we made a midline incision measuring approximately 1 cm from the inion to the upper cervical region. Blunt dissection was performed using the open-scissors technique to dissect through the muscles to the atlantooccipital membrane. Using an 18-gauge needle, we created a small hole in the atlantooccipital membrane; the hole was verified by the release of cerebrospinal fluid. A piece of polyethylene tubing (PE-10) was coated with silicon spray (Siliclad; Clay Adams, Parsippany, NJ) and advanced 8.1 cm from the insertion site to the rostral margin of the lumbar enlargement, through the slit at the atlantooccipital membrane. The catheter was fastened to the skull with dental acrylic. The incision was closed with 4-0 nylon interrupted vertical mattress sutures.

Seven days after the ligation surgery, cold-floor allodynia and pressure hyperalgesia tests were used to verify the generation of signs of neuropathic pain. In the cold-floor ambulation test, symptomatic animals raised their affected hind limbs from the chilled surface on which they were standing as a correlate measure of their cold-related allodynia. The rats were placed on a 0.13-in-thick aluminum floor, which had been chilled to \(-4^\circ\) C by an underlying freezer. This temperature does not evoke pain-related responses from healthy rats. An event recorder was used to measure the frequency
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Fig. 3. Graph demonstrating antagonist’s inhibition of the analgesic effect of tizanidine on contralateral paw pinch. Values show the mean maximum percentage of effectiveness (± SEM) on contralateral paw pinch of tizanidine, which was intrathecally administered after the intrathecal administration of the antagonist yohimbine, prazosin, or WB4101. There was no statistically significant difference among the three antagonists according to ANOVA. Each point represents between five and nine rats.

Fig. 4. Graph depicting antagonist’s inhibition of the analgesic effect of tizanidine on affected paw pinch, best-fit logarithmic curves. Values show the mean maximal percentage of effectiveness on affected paw pinch of tizanidine, which was intrathecally administered tizanidine after the intrathecal administration of the antagonist yohimbine, prazosin, or WB4101. Each point represents between five and nine rats.

and duration of paw withdrawal from the cold floor during a 20-minute period.

In the paw-pinch testing paradigm, rats withdrew their paws from a pinching stimulus as a correlate measure of their hyperalgesia in response to pressure. Increasing pressure was gradually applied to the dorsal side of the affected hind paw by using a graded motor-driven device (Ugo Basile, Milan, Italy). The pressure (in grams) at which limb withdrawal occurred was recorded. Four measurements were obtained at 3-minute intervals so that each paw was tested every 6 minutes. Rats with CCI that exhibited a higher sensitivity in the affected paw during either of these two tests were used in our experiment.

Following a baseline assessment, the animals randomly received a bolus intrathecal injection of 70% dimethyl sulfoxide in saline (vehicle for antagonists); 5, 25, 50, or 100 µg prazosin, 5, 23, or 46 µg yohimbine; or 5, 45, or 90 µg WB4101 in a 10-ml volume. The selection of these doses was based on prior studies in which these antagonists were intrathecally administered. The rats were left alone for 30 minutes to ensure maximal binding of the antagonist, after which they each received a bolus intrathecal injection of 50 µg tizanidine in a 10-ml volume. Thirty minutes after the injection, the pain tests were repeated.

Analysis of variance followed by post hoc t-tests were used to determine if the dose–response curves of the three drugs—prazosin, yohimbine, and WB4101—differed to a statistically significant degree. Exponential curves were fit to the data and the IC50 values for each of the antagonists were determined from the curve formulas.

Results

During the cold-floor ambulation test, yohimbine inhibited the analgesia induced by intrathecally administered tizanidine more than prazosin, and prazosin inhibited the analgesia more than WB4101 (Fig. 1). Nevertheless, the dose–response curves did not differ to a statistically significant degree (yohimbine compared with prazosin: F(2,32) = 3, p > 0.05; prazosin compared with WB4101: F(1,19) = 4.4, p > 0.05).

Regarding the paw-pinch test there were significant differences between the dose–response curves for the affected paw depending on antagonist and dose (Fig. 2). The dose–response curve for yohimbine differed from that for prazosin, as demonstrated by ANOVA (F(2,35) = 4.3, p < 0.05).

According to the post hoc t-test, however, the difference was statistically significant only at 119-nM doses (t = 4.7, p < 0.001). The dose–response curves for prazosin and WB4101 also differed (F(1,19) = 6.6, p < 0.05). Again, the post hoc t-tests only showed significance at 119-nM doses (t = 2.9, p < 0.05).

During the paw-pinch test on the contralateral paw, no baseline analgesia was produced by the intrathecally administered tizanidine. This phenomenon has been consistently observed with intrathecally administered tizanidine in this model of pain when performing these pain tests and, therefore, it could be that there was no inhibition because there was no analgesia to be inhibited (Fig. 3). The dose–response curves for the various antagonists on the contralateral paw-pinch test were not statistically different (tizanidine compared with prazosin F(2,35) = 1.8, p > 0.05; prazosin compared with WB4101 F(1,19) = 1.5, p > 0.05).

The estimated IC50 values for the three α2-adrenergic antagonists were as follows: yohimbine, 9.78 nM; prazosin, 13.6 nM; and WB4101, 92.3 nM. These concentrations were determined by applying logarithmic curves that fit the antagonist data for the affected paw pinch (Fig. 4). Logarithmic curves were used because they followed a typical pattern of antagonist inhibition; compared with a straight line, the logarithmic curves had the least amount of error in estimating the series of points. The antagonist doses at which the antinociceptive effect of tizanidine was half maximal were calculated using equations for the logarithmic lines. These values were reported as the IC50 for each antagonist.

The Schild regression was used to calculate the equilibrium dissociation constant (pKs) for the three antagonists. The calculated pKs were the following: yohimbine, 0.192; prazosin, 0.248; and WB4101, 47.4.

Discussion

In this study, we used two α2-adrenergic receptor subtype–specific antagonists, prazosin and WB4101, and one high-affinity α2-adrenergic receptor–specific antagonist,
yohimbine, to determine the \( \alpha_2 \)-adrenergic subtype specificity of intrathecally administered tizanidine-induced analgesia in the treatment of CCI-related neuropathic pain. The resulting antagonist profiles for the cold-floor ambulation and affected paw-pinch tests were more consistent with the binding profile of the \( \alpha_2 \)-adrenergic receptor subtype than those of the \( \alpha_1 \)- or \( \alpha_3 \)-adrenergic receptor subtype. The antagonists had no significant effect on the contralateral paw-pinch test, but this was expected because at the dose used tizanidine has repeatedly demonstrated no analgesia for pinch on the contralateral normal paw. This test of the contralateral paw pinch serves as a negative control, demonstrating that the antagonists do not have independent effects on the responses to these tests but rather act only as antagonists of tizanidine-induced analgesia. An \( \alpha_2 \)-adrenergic receptor subtype specificity for the analgesic effect of intrathecally administered tizanidine in rats with CCI may indicate the possible involvement of dorsal root ganglia because the \( \alpha_2 \)-adrenergic receptor subtype is essentially absent in the spinal cord\(^{14,18,39,48} \) but is present in dorsal root ganglia\(^{14,33} \).

The data used for determining receptor subtype involvement came from the paw-pinch test on the affected paw. The first determination was that the analgesic effect of intrathecally administered tizanidine was mediated through \( \alpha_2 \)-adrenergic receptors, not \( \alpha_1 \)-adrenergic receptors. The dose–response curve of concentrations at which prazosin inhibited intrathecally administered tizanidine-induced analgesia was higher than the dose–response curve for yohimbine. Yohimbine has a higher affinity for \( \alpha_2 \)-adrenergic receptors than for \( \alpha_1 \)-adrenergic receptors. The antagonist effect of yohimbine was consistent with an \( \alpha_2 \)-adrenergic antagonist, whereas prazosin is a specific \( \alpha_2 \)-adrenergic antagonist. Yohimbine has a much higher affinity for \( \alpha_2 \)-adrenergic receptors than for \( \alpha_1 \)-adrenergic receptors, and prazosin has a much higher affinity for \( \alpha_1 \)-adrenergic receptors than for \( \alpha_2 \)-adrenergic receptors. The antagonist effect of yohimbine at much lower doses than prazosin was consistent with an \( \alpha_2 \)-adrenergic receptor site of action for the antinociception produced by intrathecally administered tizanidine. These results were consistent with those of many studies of \( \alpha_2 \)-adrenergic antinociception at the spinal level, which have shown that the effect is mediated by \( \alpha_2 \)-adrenergic receptors.\(^{14,33,34,35} \)

A comparison of the IC\(_{50}\) results for prazosin and WB4101 indicated that the antinociceptive effect of intrathecally administered tizanidine was mediated through the \( \alpha_2 \)-adrenergic receptor subtype. Prazosin and WB4101 act as antagonists at \( \alpha_2 \)-adrenergic receptors at low doses, but at higher doses they act as antagonists at \( \alpha_2 \)-adrenergic receptors. The binding characteristics of prazosin and WB4101 can differentiate between the subtypes of \( \alpha_2 \)-adrenergic re-

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**TABLE 1**

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<th>Authors &amp; Year</th>
<th>Source</th>
<th>Tissue Type</th>
<th>Bind C</th>
<th>( \alpha_2 )</th>
<th>Yoh‡</th>
<th>Praz‡</th>
<th>WB‡</th>
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<th>WB/Praz Ratio</th>
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* \( \alpha_2 \) = \( \alpha_2 \)-adrenergic receptor subtype; Bind C = binding constant; CL = cell line; G = genetic clone expressed in a cell line lacking the \( \alpha_2 \)-adrenergic receptor; Praz = prazosin; T = tissue preparation; WB = WB4101; Yoh = yohimbine.
† The binding constant column indicates the binding constant that was used, either the inhibitory constant (K\(_i\)) or the dissociation constant (K\(_d\)).
‡ These values represent constants.

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**Fig. 5.** Comparison of antagonist ratios from the paw-pinch test and ratios from binding data. The labels 2A, 2B, 2C, 1A, and 1B all refer to the means for the binding ratios of \( \alpha_2 \)-adrenergic receptor subtypes based on receptor preparations described in the existing literature. Labels 2A, 2B, and 2C are presented with their SEMs. Paw-pinch data were obtained from the current study. Data from tail-flick and hotplate tests (asterisks) were obtained from another study in which these antagonists were intrathecally administered and their effects on normal nociception were determined.
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cptors. Prazosin is an α2-adrenergic antagonist at lower concentrations than WB4101, and WB4101 is an α2-adrenergic antagonist at lower concentrations than prazosin. Both prazosin and WB4101 are α2-adrenergic antagonists at intermediate concentrations. Table 1 presents the antagonist profiles of yohimbine, prazosin, and WB4101 with various α2-adrenergic receptor preparations.

Because the α2-adrenergic receptor subtype can be determined by comparing the concentrations at which these three drugs act as antagonists, the IC50 ratios for prazosin/yohimbine and WB4101/prazosin were graphed in Fig. 5. The means and SEMs for the α2α2, α2α2, and α2α2-adrenergic receptor preparations were obtained from the existing literature and included along with the ratios of the IC50 values of the antagonists used in the present study’s paw-pinch results.

The majority of the binding data from receptor preparations in the existing literature is presented in the form of inhibitory constants. The formula for the inhibitory constant is Ki = IC50/(1 + C/Kd), where Ki is the inhibitory constant for each antagonist, IC50 is the concentration of the antagonist that inhibits 50% of agonist activity, C is the concentration of the agonist, and Kd is the dissociation constant of the agonist at the receptor.12 The IC50 values for the antagonists were calculated from data in this study. Because the agonist was tizanidine for all experimental groups, the C and Kd were constant and the ratio of two antagonists’ Kd values for a given receptor subtype should be the same as the ratio of those two antagonists’ IC50 values for the same receptor subtype. For these reasons, the ratios of the IC50 values for the antagonists in this study were compared with the ratios of Kd values for the same antagonists with standard receptor subtype preparations obtained from the existing literature.

The ratios of the antagonist’s effects from this study were plotted on the same graph as the means and SEMs for the α2α2, α2α2, and α2α2-adrenergic receptor preparations, which were obtained from the existing literature (Fig. 5). The paw-pinch antinociception produced by intrathecally administered tizanidine had an antagonist binding profile that most closely matched the α2α2-adrenergic receptor subtype. The results of the cold-floor amputation test of allodynia had similar relationships. The antagonist efficacies in descending order were yohimbine, prazosin, and WB4101; however, the differences did not reach statistical significance and did not allow for the calculation of the IC50 values of the antagonists. We interpreted these results as indicating that the analgesia for neuropathic pain that was induced by intrathecally administered tizanidine was mediated through the α2α2-adrenergic receptor subtype.

In a study by Sagen and Proudftit,38 the same antagonists used in the present study were intrathecally administered to cover the dorsal root ganglion, placing it in the subarachnoid space,11 and thus the dorsal root ganglion would be exposed to intrathecally administered agents. The α2α2-adrenergic receptor subtype is present in the dorsal root ganglion.14 Many changes have been found in affected dorsal root ganglia of rats with the CCI model of neuropathic pain. More recently, intrathecally administered tizanidine may produce analgesia by stimulating α2α2-adrenergic receptors in the dorsal root ganglia.37 These findings support the involvement of the dorsal root ganglion in neuropathic pain. Intrathecally administered tizanidine may produce analgesia by stimulating α2α2-adrenergic receptors in the dorsal root ganglia.

Conclusions

This study has provided evidence that the antinociception produced by intrathecally administered tizanidine is mediated by the α2α2-adrenergic receptor subtype. This is consistent with other reports that tizanidine is an α2α2-adrenergic agonist and that normal endogenous α2α2-adrenergic antinociception is mediated through the α2α2-adrenergic receptor subtype.36 These findings raise the possibility that the α2α2-adrenergic receptor may be upregulated in the spinal cord of neuropathic pain.
rats with CCI or that intrathecally administered tizanidine acts at the dorsal root ganglion rather than in the spinal cord.

References
12. Cheng Y, Prusoff WH: Relationship between the inhibition constant (K1) and the concentration of inhibitor which causes 50 percent inhibition (I50) of an enzymatic reaction. Biochem Pharmacol 22:3099–3108, 1973
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Address reprint requests to: James W. Leiphart, M.D., Ph.D., Department of Neurosurgery, George Washington University, 2150 Pennsylvania Avenue, NW, Suite 7-420, Washington, DC 20037. email: jleiphart@mfa.gwu.edu.