Analysis of Drug Interaction between Intrathecal Clonidine and MK-801 in Peripheral Neuropathic Pain Rat Model

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Background: Spinally delivered $\alpha_2$-adrenoceptor agonists and $N$-methyl-D-aspartate antagonists each have been shown to have actions attenuating the hyperesthesia in rat models of nerve injury pain. Using a fixed-dose analysis and an isobolographic paradigm, the spinal interaction between the $\alpha_2$-adrenoceptor agonist clonidine and the $N$-methyl-D-aspartate antagonist MK-801 is characterized in a rat model of nerve injury-induced tactile hyperesthesia.

Methods: Male Sprague Dawley rats were anesthetized with halothane, and the left L5 and L6 spinal nerves were ligated (Chung model). After 7–10 days' recovery, a Polyethylene tubing catheter was implanted into the lumbar intrathecal space. After recovery from catheter implantations (5–7 days), intrathecal dose-response curves were established for the antihyperesthesia effects of clonidine (3, 6, 10, and 20 $\mu$g) and MK-801 (1, 3, 10, and 20 $\mu$g) alone to obtain the ED$_{50}$ for each agent. In separate studies, three doses of clonidine (1, 3, and 10 $\mu$g) were injected mixed with one dose of MK-801 (1 $\mu$g) for fixed-dose analysis, and three doses of the two agents (2, 6, and 20 $\mu$g) were injected jointly in a fraction of the dose ratio 1:1 for isobolographic analysis. Thresholds for left hind paw withdrawal to von Frey hair application were assessed.

Results: Rats with nerve ligation showed a reliable tactile hyperesthesia (mechanical threshold 1–3 g vs. normal >15 g). Intrathecal clonidine and MK-801 alone produced dose-dependent reductions of tactile hyperesthesia: ED$_{50}$ 9 $\mu$g and 10 $\mu$g, respectively. With the fixed-dose analysis, the log dose-response curves showed a left shift that considerably exceeds the theoretical curve made by a simple sum of the effects of clonidine alone and with MK-801 (1 $\mu$g). With the isobolographic analysis, the combination ED$_{50}$ was found to be statistically less than the theoretical additive dose combination. Intrathecal atipamezole, an $\alpha_2$ antagonist, reversed the effects of clonidine and the clonidine/MK-801 mixture but not MK-801 alone. The side effect of clonidine was sedation and urination and that of MK-801 was motor weakness at doses above 10 $\mu$g. These effects were considerably less severe in rats after equitactive doses in the combination group.

Conclusions: The neuropathic pain is mediated by low-threshold mechanoreceptors, sympathetically dependent, and sensitive to both $\alpha_2$ agonists and $N$-methyl-D-aspartate antagonists. Intrathecal clonidine may act to diminish sympathetic outflow, whereas MK-801 blocks the $N$-methyl-D-aspartate receptor that is associated with other spinal systems related to pain transmission mechanisms. The two separate mechanisms may account for the powerful synergy observed in this study. Such combinations might be useful in neuropathic pain states to potentiate the antihyperesthetic effects and to reduce the side effects of each agent. (Key words: Measurement techniques: fixed-dose analysis; isobolographic analysis. Pain: neuropathic. Sympathetic neurons system, $\alpha_2$-adrenoceptor agonist: clonidine. Sympathetic neurons system, $\alpha_2$-adrenoceptor antagonist: $N$-methyl-D-aspartate MK-801.)

After peripheral nerve injury in humans, a syndrome of events may be observed that includes a marked pain state evoked by a low-threshold tactile stimulus (e.g., allodynia) and dependency of this pain state on intact sympathetic function.1 Recent laboratory work has led to an increased understanding of the mechanisms that may underlie this syndrome. Thus, ligation of the L5–L6 nerve roots in the rat will produce marked allodynia and thermal hyperalgesia that are reversed by sympatheticom.2 It has been shown that sural nerve section and ligation triggers central sprouting of large myelinated afferents into the upper laminae of the dorsal horn.3 Of additional interest, it has been shown that, after sciatic nerve ligation and transection, catecholamine-containing terminals sprout into dorsal root ganglia and form basket-like structures around large-diameter axotomized sensory neurons and that, subsequently, preganglionic sympathetic stimulation can activate primary afferents in that root.4

Intrathecally administered $\alpha_2$-receptor agonists are known to exert a potent sympatholytic effect by a direct action on spinal preganglionic sympathetic neurons.5

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In recent studies, it has been shown that spinal α₂ agonists will diminish the tactile hyperesthesia observed in rats after peripheral nerve lesion. A finding consistent with reports that spinal clonidine attenuates sympathetically maintained pain in humans. The observation that peripheral nerve injury may yield enhanced neuronal input (e.g., spontaneously active neumag and ganglion cells) and may induce postsynaptic change that leads to altered inhibitory function in the dorsal horn has led to the speculation that the postnerve injury hyperesthesia may reflect an example of facilitated discharge of wide dynamic range neurons (windup) in spinal cord, mediated in part by the activation of a spinal N-methyl-D-aspartate (NMDA) receptor. Potential changes in dorsal horn organization, leading to a loss of local inhibition, also may account for this altered encoding of the sensory message. Thus, the spinal delivery of GABA and glycine antagonists produces a severe touch-evoked agitation, and this effect was blocked by spinal NMDA receptor antagonists. Subsequent studies further demonstrated that the tactile hyperesthesia resulting from nerve injury also can be blocked by spinal NMDA receptor antagonists.

Given that post-nerve injury nociceptive behaviors are maintained both by sympathetic nerve activity and by NMDA receptor activation, an important issue is the nature of the interaction of these two mechanisms. If the role played by the NMDA receptor is strictly dependent on the activity purportedly induced by preganglionic sympathetic neurons, it is possible that the two classes of agents interact in at most an additive manner, e.g., the smaller the sympathetic drive, the smaller the role played by the NMDA receptor. On the other hand, if the two systems are organized separately, they may interact in a synergistic (greater than additive) or occlusive (less than additive) fashion. Aside from the theoretical significance of this interaction, synergy between classes of agents with nonoverlapping side effects has particular clinical importance. The major side effect of clonidine is sedation, related to its supraspinal redistribution and hypotension mediated by a spinal action and that of MK-801 is motor weakness. The characteristics of the antihyperesthesia interaction of the two classes of agents is of potential clinical significance, as joint use may serve to reduce the incidence of side effects produced by each class of agents.

In this study, we evaluated, using a fixed-dose analysis and an isobolographic paradigm, the nature of the spinal interaction between the α₂-adrenoceptor agonist clonidine and the NMDA receptor antagonist MK-801 in attenuating the tactile hyperesthesia induced by ligation of the L5–L6 spinal nerve root of rat.

**Methods**

**Animal Preparation**

The following investigations were carried out under a protocol approved by the Institutional Animal Care Committee, University of California, San Diego.

**Neuropathic Model.** Male Sprague-Dawley rats (weight 120–140 g; Harlan Industries, Indianapolis, IN) were housed in the vivarium and allowed to acclimate for 3–5 days using a 12/12 h day/night cycle. For creating the neuropathic rat model, the surgical procedure was performed according to the previous description by Kim and Chung. Briefly, under halothane anesthesia (1% in air/O₂, 50/50), a partial excision of left transverse process was made, and the left L5 and L6 spinal nerves were isolated and ligated tightly with 6-0 silk suture just distal to the dorsal root ganglion and proximal to the formation of the sciatic nerve. After a 7–10-day postoperative recovery period, the intrathecal catheter is placed.

**Implantation of Intrathecal Catheters.** For spinal drug administration, rats were chronically implanted with catheters as previously described. Briefly, under halothane anesthesia, the rat was placed in a stereotaxic head holder. The occipital muscles were separated from their attachment point and retracted caudal to expose the cisternal membrane at the base of the skull. Polyethylene tubing was passed caudally from the cisterna magna to the level of lumbar enlargement (S.5 cm). Animals with evidence of neuromuscular dysfunction were promptly killed.

**Testing**

**Hyperesthesia.** For testing, the animals were placed individually in plastic cages with a wire mesh bottom. Behavioral accommodation was allowed for approximately 15 min until cage exploration and major grooming activities ceased. To test the tactile threshold required to evoke withdrawal of the stimulated paw, von Frey hair was applied to the paw of the ligated...
nerve (left) vertically for 3 or 4 s while the hair was bent a little. The area tested was the midplantar left hind paw, avoiding the tori (foot pads), in the sciatic nerve distribution. The 50% withdrawal threshold was determined using the up-down method initiating with the 2.0-G hair, in the middle of the series of 8 von Frey hairs with logarithmically incremental stiffness (0.41–15.1 g). The resulting pattern of responses is tabulated and the 50% response threshold computed using the formula \( \log (\text{threshold}, \text{mg} \times 10) = X_t + kd \), where \( X_t \) = value \((\text{in log units})\) of the final von Frey hair used, \( k \) = correction factors based on pattern of responses from calibration table, and \( d \) = mean difference in log units between stimuli (here 0.224).

**Side Effects.** After injection, general posture and ambulation were noted. Severe sedation was defined as a significant decrease in spontaneous activity and a loss of the orienting response to light stimulation. To study the motor abnormality of hind limb function, the absence of placing and stepping reflex (flaccidity) was noted as an index of motor weakness. The placing and stepping responses of the hind limb were assessed by dragging the dorsum of the right unligated paw over an edge. This normally evokes a lifting and placing movement of the paw.

**Drugs**

Drugs employed were clonidine hydrochloride (molecular weight 267; Boehringer Ingelheim), MK-801 ((5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate, dizocilpine; molecular weight 337; RBI), and atipamezole (molecular weight 249; FARMOS). Drugs were dissolved in saline and prepared to be delivered in a volume of 10 \( \mu l \) saline. The intrathecal drug administration is followed immediately by 10 \( \mu l \) saline to flush the catheter. Animals were randomly assigned to receive up to three different doses or drugs, with testing carried out at intervals of 5–7 days.

**Experimental Paradigm**

**Dose-Response Curve.** The first series of experiments was performed to determine the dose-response and time course of intrathecally administered clonidine and MK-801. On the basis of preliminary studies, four dose levels of each clonidine (3, 6, 10, and 20 \( \mu g \)) and MK-801 (1, 3, 10, and 20 \( \mu g \)) were examined to determine the dose that produced a %MPE of 50% \((ED_{50})\).

**Drug Interaction.** The second series of experiments was performed using the fixed-dose analysis and the isobolographic analysis to determine the drug interaction between clonidine and MK-801, as previously described. The fixing-dose analysis, we added a given dose of MK-801 (1 \( \mu g \)) in combination with clonidine 1, 3, or 10 \( \mu g \). If the log dose-response curve for clonidine shows a left shift that exceeded the shift in the theoretical curve for clonidine produced by the simple addition of the effects produced by MK-801 1 \( \mu g \) alone, the interaction of the two drugs is defined as suprallicative or synergetic.

Using the isobolographic analysis, we determined the effects produced when combinations of intrathecal clonidine and MK-801 were jointly delivered such that the doses were a fixed fraction of the dose ratio (1:1) but did not exceed 10 \( \mu g \) because of the flaccidity that began to appear with this dose of MK-801 alone. In this manner, we calculated the dose combination that yielded an \( ED_{50} \). The isobols were drawn by plotting the experimentally determined \( ED_{50} \) value of clonidine on the Y axis and that of MK-801 on the X axis delivered alone and in combination. The theoretical \( ED_{50} \), assuming simple additivity and variance, was calculated according to the equation described by Tallarida et al.

**Antagonist.** To determine whether the effects of intrathecal clonidine alone and with MK-801 or MK-801 alone were mediated by an interaction with an \( \alpha_2 \) receptor, the \( \alpha_2 \)-adrenoceptor-selective antagonist (atipamezole 20 \( \mu g \)) was delivered intrathecally 10 min before injection of the clonidine (20 \( \mu g \)), MK-801 (10 \( \mu g \)), or combination of two agents (10 + 10 \( \mu g \)).

**Data Analysis and Statistics**

Threshold data from von Frey hair testing were converted to %MPE according to the formula

\[
\%\text{MPE} = \left( \frac{\text{post drug threshold} - \text{baseline threshold}}{\text{cutoff threshold} - \text{baseline threshold}} \right) \times 100.
\]

The cutoff value was defined as stimulus intensities of 15 g \((i.e., \%\text{MPE} = 100)\). Dose-response and time course data are graphically presented as mean %MPE ± SEM. The \( ED_{50} \) values, slopes, and 95% confidence intervals are assessed using a dose-response analysis of Tallarida. Statistical comparison of the difference between the effect of agents alone and with atipamezole were performed by paired \( t \) test. Critical values that achieve probability values of \( P < 0.05 \) were considered to be statistically significant.
Fig. 1. Time-dependent reduction in tactile hyperalgesia (expressed as %MPE) produced by intrathecal injection of clonidine (CLON; top), MK-801 (MK; middle), and clonidine combined with MK-801 (CLON + MK; bottom) given in the doses indicated. Each line represents the mean %MPE with SEM bars in five or six rats.

Results

General Appearance
After nerve ligation, all rats displayed normal general behavior and weight gain. The lesioned paw showed mild deformity and nail growing. Nevertheless, testing revealed that, after nerve ligation, all animals showed a marked tactile hyperalgesia, as evidenced by the ability to evoke a brisk withdrawal response with the von Frey hair, such that baseline mechanical thresholds required to evoke a brisk withdrawal of the stimulated paws before treatment were in the range of 1–3 g for all rats.

Dose-Response Curve
The intrathecal administration of either clonidine or MK-801 resulted in a dose-dependent increase in the mechanical threshold for tactile evoked withdrawal of the stimulated paw, with the peak effect of either drug occurring within 30 min (figs. 1 and 2). The ED_{50} values, slopes, and 95% confidence intervals for clonidine and MK-801 are presented in table 1.

Drug Interaction
The log dose-response curve of clonidine mixed with the fixed dose of MK-801 was shifted to the left as compared to that of clonidine without MK-801. The ED_{50} value of clonidine joined with 1 μg MK-801 was less than that of the ED_{50} of clonidine alone as calculated when the %MPE value of 1 μg (6%) MK-801 was added (fig. 2).

Table 1. ED_{50} (μg) and Slope with 95% CI for Dose–Response Curve of Intrathecal Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>ED_{50} (95% CI)</th>
<th>Slope (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>23</td>
<td>9 (7–11)</td>
<td>88 (60–117)</td>
</tr>
<tr>
<td>MK-801</td>
<td>22</td>
<td>10 (5–17)</td>
<td>49 (28–69)</td>
</tr>
<tr>
<td>Clonidine*</td>
<td>17</td>
<td>2 (2–3)</td>
<td>38 (25–50)</td>
</tr>
</tbody>
</table>

N = number of rats employed in constructing the dose–response curve; CI = confidence interval.

* ED_{50} and slope for clonidine dose–response curve when mixed with 1 μg of MK-801.
INTERACTION BETWEEN INTRATHecal CLONIDINE AND MK-801

Fig. 3. Isobolographic plot for the interaction between intrathecal clonidine (CLON) and MK-801 (MK). The ED_{so} values for each agent are plotted on the Y and X axes, respectively, and the thick lines present the SEM of the ED_{so}. The dotted line connecting these two points is the theoretical line of additivity. The theoretical additive ED_{so} point (A) is calculated from the ED_{so} values and 95% confidence intervals (CI) of each agent. The experimental ED_{so} point (B) for the combinations lies within the space defined by the theoretical line of additivity. The confidence intervals do not overlap, indicating a supra-additive interaction.

Dose-response curves were generated with the two drugs being given in the fixed fraction of the dose ratio 1:1. The intrathecal administration of the combination doses resulted in a dose-dependent increase in the mechanical pain threshold. The isobolographic analysis indicated that there was no overlap between the confidence intervals of the experimentally determined combination ED_{so} and the theoretic line of additivity, showing that the drug interaction is synergistic (fig. 3). The dose-sparing ratio (the sum the ratios of the ED_{so} values for MK-801 and clonidine determined alone and jointly) was calculated to be 0.46.

α2 Antagonist
The intrathecal delivery of atipamezole had no effect on the antihyperesthesia effects of approximately equiactive doses of intrathecal MK-801 but significantly attenuated the effect of clonidine alone and clonidine given together with MK-801 (P < 0.05; fig. 4).

Side Effects
Spinal injection of clonidine resulted in a dose-dependent incidence of sedation with exophthalmus and significant urinary voiding. Prominent sedation was observed at 20 μg.

Detectable flaccidity with MK-801 was not observed until an injection of 20 μg. All rats became too weak to walk and could not respond to von Frey hair application at the dose of 30 μg, limiting the highest dose that could be used of this agent. All of the weakness, even that produced by the highest dose, was resolved by 24 h. Side effects were considerably less severe after equiactive doses in the combination group (table 2).

Table 2. Summary of Incidence of Side Effects after Intrathecal Clonidine, MK-801, and Clonidine and MK-801 Together

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (μg)</th>
<th>N</th>
<th>Motor Weakness</th>
<th>Severe Sedation</th>
<th>Urination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>6</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>MK-801</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>17</td>
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<tr>
<td></td>
<td>20</td>
<td>5</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>5</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MK-801 + clonidine</td>
<td>3 + 3</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 + 10</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>10 + 10</td>
<td>6</td>
<td>33</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

Values of side effects are percent of rats showing response.

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Discussion

Hyperesthesia

Tactile allodynia, which is partly dependent on sympathetic activity for its manifestation, is a conspicuous component of the post-nerve injury pain state in humans. Such pain states often are found to show minimal sensitivity to systemically or spinally delivered opiates. The ligation of the L5–L6 nerve root in the rat, as described by Kim and Chung, results in a syndrome with particular similarities to the human clinical pain state: a clear escape response is evoked by a low-intensity tactile stimulus; the hyperpathia and thermal hyperalgesia are reversed by sympathectomy, and spinal opiates have only modest effects on the tactile hyperesthesia. As reviewed in the introduction, laboratory studies employing such models have emphasized the role of anomalous sprouting of large myelinated afferents into the dorsal horn, possible loss of dorsal horn interneurons, and the sprouting of sympathetic terminals in the dorsal root ganglion of the injured nerve along with the development of a local sensitivity to sympathetic input.

The observation that intrathecal clonidine and NMDA receptor antagonists can ameliorate this pain state in animal models of tactile hyperesthesia is important in that it implicates a role for these several receptor systems in regulating this pain state and suggests their likely importance in the behaviorally similar states observed in humans. Reports have indicated that epidural clonidine can diminish neuropathic symptoms in RSD pain states, whereas an intrathecal NMDA antagonist was shown to diminish the hyperesthetic component resulting from repetitive tactile stimulation in a nerve-injured patient.

Clonidine

Spinal α2 agonists can alter pain transmission by acting presynaptically on C fibers to reduce transmitter release, as well as acting postsynaptically to hyperpolarize dorsal horn nociceptors. However, this does not appear to be the explanation for the actions of spinal α2 agents. Such an alternative would suggest that spinal opioids would be equally efficacious only if they act on the same synapses in this model, but they are not. Although other alternatives exist, it appears likely that the antihyperesthetic action reflects on the sympathetic dependency of this model and the ability of spinal α2-adrenoceptor agonists to inhibit sympathetic outflow. Thus, intrathecal α2 agonists reduce sympathetic output and decrease blood pressure by a direct effect on spinal sympathetic preganglionic neurons. Studies have shown that the antihyperesthesia effects are mediated at the level of the thoracolumbar spinal cord.

MK-801

With regard to MK-801, this agent exerts a well known action as a noncompetitive NMDA receptor antagonist. Its actions in this model are not likely due to a direct blockade of afferent input. Previous studies have emphasized that the NMDA receptor is not postsynaptic to the primary afferent but is postsynaptic to an interneuron that is responsible for the evocation of a facilitated state of afferent processing, as manifested in the discharge of dorsal horn wide dynamic range neurons. These observations are consistent with several lines of observations suggesting that these states are mediated by the spinal release of glutamate. Thus, the spinal delivery of NMDA will enhance the response of dorsal horn neurons to low-threshold mechanical stimuli and evoke a state of exaggerated responses to low-threshold tactile stimuli (e.g., tactile allodynia). Conversely, in several models, it has been shown that NMDA antagonists are able to attenuate the facilitated component of the pain state. Moreover, in models in which tactile hyperesthesia can be induced, i.e., after the spinal delivery of strychnine, and in the Chung model of neuropathy, spinal NMDA antagonists are able to attenuate significantly the tactile hyperesthesia. This supports the evolution of a role for NMDA receptors in the miscoding of the sensory message in the absence of glycine inhibition or with the dorsal horn reorganization associated with peripheral nerve injury. Alternatively, it should be noted that NMDA antagonist may reduce excitatory input on IML neurons and attenuate sympathetic output. It is thus possible that a component of its actions also relates to a reduction in sympathetic outflow. However, NMDA antagonists, unlike α2 agonists, can exert antihyperesthesia effects by the mechanisms that do not likely involve sympathetic dependency (e.g., as after the acute delivery of intrathecal strychnine).

Synergy

A variety of drug classes have been shown to be associated with a synergistic interaction, as reflected by their analgesic activity. It is possible that the aug-

§ Chapin, Bach: Unpublished observations.

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mented activity resulted from a decreased clearance. Although not examined in this study, we previously showed that spinal $\alpha_2$ agonists do not alter the spinal clearance of other spinal agents, such as morphine. Moreover, there was no apparent decrease in the time of peak effect or increase in the duration of action, as might be anticipated if the mechanisms of enhancement were related to a simple change in clearance. Alternatively, the two agents may have acted to augment the affinity of the other agent for its receptor. Although there are no binding data to refute such synergy, we note that the side effects of either agent were not enhanced. Were there to be a receptor interaction, we would anticipate that the appearance of sedation and urination (with clonidine) or the motor weakness (with MK-801) would have been similarly enhanced. Failure to see such enhancement likely would exclude a facilitation of the receptor interaction. We thus conclude that the augmentation likely reflects the nature of the interaction between the hypothesized reduction in sympathetic outflow and the role played by NMDA receptors in the dorsal horn after peripheral nerve lesion. We can only speculate that, to the degree that the acute reduction in sympathetic outflow reduces the component that evokes a state of facilitated processing, the level of glutamatergic tone activating the segmental NMDA receptor is correspondingly reduced and the levels of NMDA antagonists to "normalize" the pain state are significantly diminished. This positive interaction, predicated on the distinct spinal mechanisms by which these two classes of agents act, may possess clinical significance in the management of pain states with a sympathetic dependency.

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