

Intrathecal Amitriptyline Acts as an N-Methyl-D-Aspartate Receptor Antagonist in the Presence of Inflammatory Hyperalgesia in Rats

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Background: Amitriptyline and other tricyclic antidepressants exhibit high affinity binding to N-methyl-D-aspartate (NMDA) receptors *in vitro* and inhibit NMDA receptor activation-induced neuroplasticity in hippocampal slices. Because spinal NMDA receptor activation is believed to be central to generation and maintenance of hyperalgesic pain, the purpose of this study was to test whether intrathecal amitriptyline reduced inflammation-induced hyperalgesia in the rat.

Methods: Rats were prepared with chronic lumbar intrathecal and femoral intravenous catheters and nociceptive threshold was assessed by hind paw withdrawal to a radiant heat stimulus. Rats received an injection of carrageenin in one hind paw followed by thermal paw withdrawal testing 3 hr later and intrathecal amitriptyline and/or intravenous morphine injection. In other rats, intrathecal NMDA injection was preceded by either intrathecal saline or 60 µg amitriptyline.

Results: Intrathecal amitriptyline reversed thermal hyperalgesia in a dose-dependent manner, but had no effect on withdrawal latency of the contralateral, noninjected paw. Intrathecal phentolamine plus methysergide did not alter amitriptyline's effect, except at the lowest dose. Intravenous morphine increased paw withdrawal latency in both inflamed and control paws in a dose-dependent fashion, and morphine interacted additively with intrathecal amitriptyline to reverse hyperalgesia. Thermal hyperalgesia induced by NMDA was completely antagonized by intrathecal amitriptyline.

Conclusions: Amitriptyline and other tricyclic antidepressants have been demonstrated to exhibit modest activity against clinical neuropathic pain after systemic administration. These data suggest that more profound pain relief might be obtained by intrathecal administration. Amitriptyline reverses hyperalgesia in rats by a mechanism unrelated to

monoamine reuptake inhibition, and likely due to NMDA receptor antagonism. (Key words: Analgesics, opioid: morphine. Antidepressants: amitriptyline. Drug interactions: synergy. Drug interaction, analysis: isobologram. Pain, chronic: hyperalgesia. Receptors, spinal cord: N-methyl-D-aspartate.)

NEUROPATHIC pain, characterized by increased sensitivity to noxious stimuli (hyperalgesia) and perception of pain to normally innocuous stimuli (allodynia) remains difficult to treat.¹ Behaviorally defined hyperalgesia and allodynia are produced in a variety of subacute animal models, including peripheral nerve injury or tissue inflammation.² Although there has been a proliferation of models, neural injury and inflammatory models do not in general differ in spinal pharmacology and physiology of resultant hyperalgesia. There is strong evidence in both types of models that sustained noxious sensory input from the interventions results in hyperalgesia that is dependent on spinal N-methyl-D-aspartate (NMDA) receptor activation. As such, intrathecal injection of NMDA receptor antagonists prevents and/or reverses hyperalgesia in such models,^{3,4} and reduction in hyperalgesia and allodynia in a patient with longstanding neuropathic pain by intrathecal injection of an NMDA receptor antagonist⁵ suggests that these models are clinically relevant.

Amitriptyline and other tricyclic antidepressants are often administered systemically to patients with neuropathic pain, and have modest efficacy, which has been presumed to be caused by inhibition of norepinephrine or serotonin reuptake.⁶ However, a structure-activity analysis fails to demonstrate a clear relationship between specific efficacy at inhibition of either norepinephrine or serotonin reuptake and analgesia.⁶ Amitriptyline and other tricyclic antidepressants show high-affinity binding to NMDA receptors,⁷ and function as NMDA antagonists⁸⁻¹¹ at concentrations similar to those inhibiting monoamine reuptake,¹² and it is conceivable that their efficacy lies in this activity rather than in monoamine reuptake inhibition.

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Amitriptyline is the only tricyclic antidepressant available commercially in a formulation not containing preservatives shown to be neurotoxic after intraspinal administration. Intrathecal amitriptyline injection causes no behavioral analgesic effect in normal animals, but synergistically enhances behavioral analgesia from intravenous morphine.¹³ This interaction is thought due to inhibition of spinal monoamine reuptake, because systemically administered opioids activate descending bulbospinal inhibitory noradrenergic and serotonergic pathways.¹⁴ The purpose of the current study was to test the hypothesis that intrathecal amitriptyline reduces behavioral hyperalgesia in rats by a mechanism involving NMDA, but not monoamine receptors, and to determine intrathecal amitriptyline's interaction with intravenous morphine in behavioral hyperalgesia.

Materials and Methods

Animals

After approval by the Animal Care and Use Committee, 31 male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 325–375 g were studied. Rats were surgically prepared during sodium pentobarbital anesthesia (40–50 mg/kg, intraperitoneally). A femoral venous catheter was implanted for morphine administration, exteriorized, and secured at the back of the head. An intrathecal catheter (PE-10 tubing) was inserted through a small opening in the cisterna magnum and passed 8.5 cm caudad in the intrathecal space. After surgery, rats were housed individually with free access to food and water and allowed to recover for at least 1 wk before use. Rats showing postoperative neurologic deficits were killed immediately.

Nociceptive Testing

The hind paw thermal withdrawal was used as previously described to test thermal antinociception. Briefly, the intrathecal and intravenous catheters were connected to PE-20 tubing and syringes prefilled with all drugs to be administered during the study, and the rats were placed in a clear plastic container on an elevated floor of clear, heat-tempered glass. After 15–30 min for the animal to become habituated to the environment, a radiant heat source (50 W halogen projector lamp, GTE Products Corp, Winchester, KY), with bulb intensity controlled by a constant voltage source, was focused on the plantar surface of one hind paw where it was in contact with the glass. Bulb intensity was ad-

justed so that the baseline latency to paw withdrawal from the heat source was 10–15 s. Both paws were tested in random order 1–2 min apart, and the average of their values was calculated. Cutoff time in the absence of a response was 30 s to avoid tissue damage.

Drugs and Their Administration

Carrageenin, morphine sulfate, and NMDA were obtained from Sigma Chemical Co. (St Louis, MO). Amitriptyline was obtained from Stuart Pharmaceutical Co. (Wilmington, DE). Phentolamine was donated by Ciba-Geigy Corp (Summit, NJ) and methysergide was donated by Sandoz Research Institute (East Hanover, NJ). All drugs were dissolved in normal saline, with pH levels between 6.2 and 7.8. All drugs except morphine were injected intrathecally over 30 s in a volume of 3 μ l followed by a 10- μ l flush. Morphine was injected intravenously in a volume of 0.3 ml followed by a 0.3-ml saline flush. In preliminary experiments, we confirmed that all drugs reached peak effects within 5–10 min and their effects were sustained for 30–45 min.

Experimental Paradigm

On study days, the rat was habituated to the testing environment, and baseline hind paw withdrawal latencies were obtained. Unilateral inflammation was induced by intraplantar injection in either right or left hind paw (choice of paw determined randomly) of 2 mg freshly prepared carrageenin in 0.1 ml normal saline. As described previously,¹⁵ carrageenin injection results in a decrease in the thermal hind paw withdrawal latency on the injected side accompanied by paw edema, with no such effects on the contralateral side. In all studies, baseline withdrawal latencies were obtained immediately before carrageenin injection, 3 hr after carrageenin, then at 5-min intervals during drug injection. Hind paw thickness at the mid-plantar level was determined before and at the end of each experiment involving carrageenin injection using a calibrated micrometer. Each rat was studied only once and was killed at the end of the experiment.

In single agonist studies, animals received cumulative dosing, at 15-min intervals, of intravenous morphine (1, 3, 7, 12 mg/kg cumulative dose) or intrathecal amitriptyline (10, 20, 60 μ g), with hind paw withdrawal latencies determined every 5 min, and values obtained at 10 and 15 min after each dose averaged for the value for that dose. In the isobolographic study, a fixed ratio combination was administered in a cumulative dose-response in the ratio 10 μ g intrathecal

amitriptyline: 1000 $\mu\text{g}/\text{kg}$ intravenous morphine. This ratio was chosen based on studies of interaction between these two treatments in normal rats.¹³

One antagonist study was performed. To test whether reversal of hyperalgesia by intrathecal amitriptyline was caused by inhibition of monoamine reuptake, animals received intrathecal saline or phentolamine, 30 μg plus methysergide, 40 μg 10 min before amitriptyline dosing.

Intrathecal injection of NMDA has been demonstrated to cause flank scratching and biting behavior and thermal hyperalgesia in the hind paws.^{16,17} To directly test the interaction between amitriptyline and NMDA receptor activation, other rats received an intrathecal injection of NMDA, 1 μg , preceded in 10 min by either intrathecal saline or 60 μg amitriptyline. Paw withdrawal latencies were determined every 5 min for 30 min after NMDA injection.

Statistics

Data are presented as mean \pm SEM. Because a cutoff value was used, data were converted to percent maximum possible effect according to the formula:

percent maximum possible effect = (observed - baseline)/(cutoff - baseline) \times 100.

Two types of data analysis were performed using the above equation. To examine the dose-dependent reversal of hyperalgesia, the baseline was considered to be the postcarrageenin baseline and the cutoff to be the hind paw withdrawal latency before carrageenin injection. To examine dose-dependent analgesic effects (increase in withdrawal latency above normal baseline), the baseline was considered to be the precarrageenin baseline and the cutoff to be 30 s. With either analysis, effective dose 50 (ED_{50}) was defined as the dose that yielded a 50% maximum effect. ED_{50} and 95% confidence intervals were calculated by a graded ED_{50} program developed at the University of Iowa.¹⁸

Isobolographic analysis at the ED_{50} level for two-way drug interactions was conducted according to the procedure of Tallarida *et al.*,¹⁹ and, in the case of interactions involving intrathecal amitriptyline, according to a modified method described by Porreca *et al.*²⁰ in which one drug lacks efficacy. Confidence intervals for each point were calculated from the variances of each component alone. The confidence intervals were evaluated for statistical significance with a Student's *t* test. A value of $P < 0.05$ was considered significant.

In addition to the earlier isobolographic analysis, an algebraic (fractional) method of drug interaction at the

ED_{50} level was used. As applied to this type of analgesic paradigm by Naguib and Yaksh,²¹ this involves the expression of the component doses of the two agents (or 3 in one case) given jointly as fractions of the doses that produce the same effect when given separately. The sum of the fractional doses is determined as

$$da/Da + db/Db,$$

where D_a and D_b are the ED_{50} values of agents a and b given alone, and da and db are the doses of a and b that, when combined, are equipotent with D_a or D_b . Values less than 1 imply a synergistic interaction, and the lower the value, the more powerful the interaction.

Results

Carrageenin injection resulted 3 hr later in a similar decrease in paw withdrawal latencies among all groups on the injected side, with no change in withdrawal latency on the contralateral paw. Similarly, the increase in paw thickness was similar among all groups regardless of treatment (table 1).

Intrathecal amitriptyline, but not saline, resulted in a dose-dependent reversal of thermal hyperalgesia, whereas neither treatment affected withdrawal latencies on the control side (fig. 1). Aside from increased time with apparent weight-bearing on the inflamed paw, intrathecal amitriptyline produced no behavioral effects on observation. Pretreatment of rats with intrathecal phentolamine plus methysergide 10 min before injection of amitriptyline did not alter amitriptyline's reversal of thermal hyperalgesia, except at the lowest dose (fig. 2).

Intravenous morphine resulted in a dose-dependent increase in thermal paw withdrawal latency in both

Table 1. Effect of Carrageenan and Treatments on Paw Thickness at the Mid-plantar Level

Treatment	Paw Thickness before Carrageenan (mm)	Paw Thickness after Carrageenan (mm)
Saline	5.4 \pm 0.18	9.7 \pm 0.38
Amitriptyline	5.0 \pm 0.25	9.7 \pm 0.45
Amitriptyline + phentolamine/methysergide	5.0 \pm 0.33	9.6 \pm 0.42
Morphine	5.2 \pm 0.14	9.2 \pm 0.40
Amitriptyline + morphine	5.3 \pm 0.13	9.3 \pm 0.21

Values are mean \pm SEM of 5-7 animals. There were no significant differences among groups.

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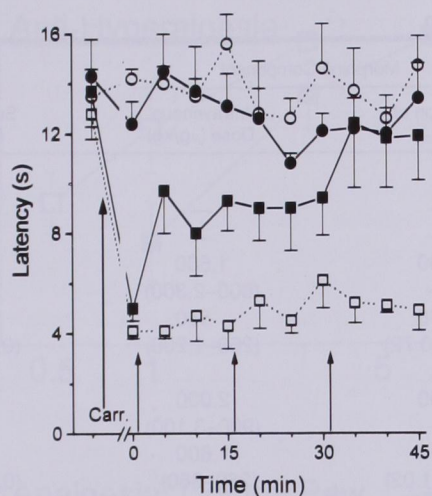


Fig. 1. Withdrawal latency before intraplantar carrageenin injection, 3 hr after carrageenin injection, and after intrathecal injection, at 15-min intervals shown by arrows, of saline (open symbols) or amitriptyline (solid symbols). Amitriptyline given escalating cumulative doses of 10, 20, and 60 μ g. Carrageenin-injected paws shown as squares, noninjected paws shown as circles. Each symbol represents the mean \pm SEM of five or six animals.

inflamed and control paws (fig. 3). Morphine was more potent, as determined by ED_{50} analysis, at reversal of hyperalgesia than at production of analgesia, and was more potent at production of analgesia on the control side than on the inflamed side (table 2). In addition to increased time with apparent weight-bearing on the inflamed paw with escalating morphine doses, the largest morphine dose also resulted in a cessation of exploring activity.

Combination of intrathecal amitriptyline and intravenous morphine resulted in an enhancement of the antihyperalgesic effect of morphine assessed on the inflamed paw (fig. 4 and table 2). Isobolographic analysis demonstrated an additive interaction in reversal of hyperalgesia (fig. 5). In contrast to this additive enhancement of morphine's effect on the inflamed paw, amitriptyline had no effect on morphine's analgesic effect to increase withdrawal latency above precarrageenin baseline to cutoff in either inflamed or noninflamed paws (fig. 4 and table 2). Behaviors after administration of intravenous morphine were unaffected by intrathecal amitriptyline injection.

Injection of 1 μ g intrathecal NMDA, resulted in spontaneous vocalization and scratching/biting of the flanks, beginning within 30 s of injection and lasting 5–20 min, as well as reduced hind paw withdrawal latency (fig. 6). Pretreatment with intrathecal amitriptyline

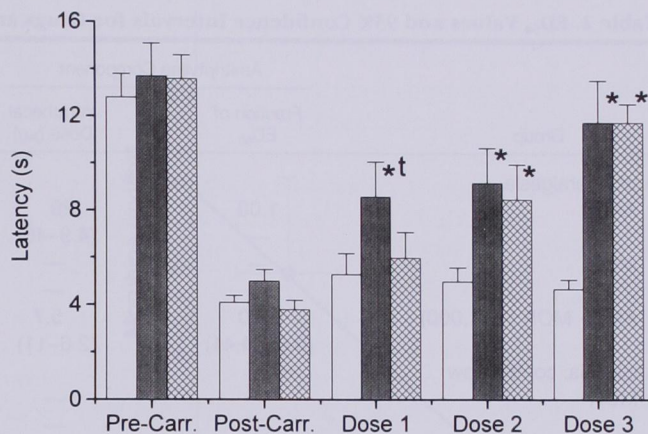


Fig. 2. Withdrawal latency before intraplantar carrageenin injection, 3 hr after carrageenin injection, and after intrathecal injection, at 15-min intervals, of saline (open bars), amitriptyline (solid gray bars) or amitriptyline after intrathecal injection of phentolamine, 30 μ g + methysergide, 40 μ g (cross-hatched bars). Amitriptyline given escalating cumulative doses of 10, 20, and 60 μ g. Each bar represents the mean \pm SEM of five or six animals. * P < 0.05 versus saline control. † P < 0.05 versus amitriptyline plus phentolamine/methysergide.

delayed the onset but did not prevent the behavioral effects of intrathecal NMDA, and completely prevented NMDA-induced thermal hyperalgesia (fig. 6).

Discussion

The current study provides several complementary lines of evidence to suggest that intrathecally admin-

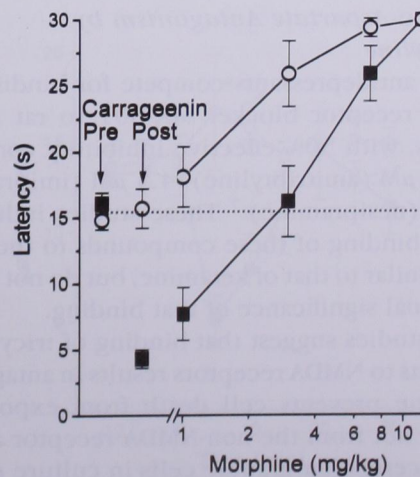


Fig. 3. Withdrawal latency before intraplantar carrageenin injection, 3 hr after carrageenin injection, and after intravenous injection, at 15 min intervals, of morphine saline. Injected paw shown in solid squares, non-injected paw shown in open circles. Each symbol represents the mean \pm SEM of six animals.

Table 2. ED₅₀ Values and 95% Confidence Intervals for Drugs and Combination

Group	Amitriptyline Component		Morphine Component		Sum of ED ₅₀ Fractions
	Fraction of ED ₅₀	Intrathecal Dose (μg)	Fraction of ED ₅₀	Intravenous Dose (μg/kg)	
Antihyperalgesia					
AMI	1.00	29	—	—	1.00
	—	(4.9–46)	—	—	—
MOR	—	—	1.00	1,500	1.00
	—	—	—	(600–2,300)	—
AMI + MOR (10:1,000)	0.20	5.7	0.38	560	0.58
	(0.09–0.41)	(2.6–11)	(0.18–0.72)	(260–1,200)	(0.27–1.13)
Analgesia: control paw					
MOR	—	—	1.00	2,000	1.00
	—	—	—	(900–3,100)	—
AMI + MOR (10:1,000)	—	1.6	0.80	1,600	0.80
	—	(1.2–2.0)	(0.61–1.02)	(260–860)	(0.61–1.02)
Analgesia: inflamed paw					
MOR	—	—	1.00	4,800	1.00
	—	—	—	(4,000–5,600)	—
AMI + MOR (10:1,000)	—	6.8	1.40	6,800	1.40
	—	(3.2–10)	(0.75–2.20)	(3,600–10,000)	(0.75–2.20)

Values are mean of 5–7 animals; 95% confidence intervals are in parentheses. AMI = amitriptyline; CLO = clonidine; MOR = morphine; NEO = neostigmine.

istered amitriptyline reverses hyperalgesia *via* spinal NMDA receptor antagonism. These data are consistent with previous observations that amitriptyline possesses potent NMDA receptor antagonist properties and that spinally administered NMDA receptor antagonists block or reverse hyperalgesic states.

N-Methyl-D-Aspartate Antagonism by Amitriptyline

Tricyclic antidepressants compete for binding with the NMDA receptor blocker MK-801 to rat cortical membranes, with 50% effective inhibitory concentrations of 57 μM (amitriptyline), 4.5 μM (imipramine), or 7.4 μM (desipramine).⁷ These studies indicate an affinity for binding of these compounds to the NMDA receptor similar to that of ketamine, but do not address the functional significance of that binding.

In vitro studies suggest that binding of tricyclic antidepressants to NMDA receptors results in antagonism. Amitriptyline prevents cell death from exposure to NMDA, but not from the non-NMDA receptor agonist, kainate, in cerebellar granule cells in culture (EC₅₀ = 7 μM)⁸ and blocks NMDA- or glutamate-induced increases in intracellular Ca²⁺ in cerebellar granule cells (range 0.5–1 μM)⁹ and cortical neurons (50% effective inhibitory concentrations = 27 μM).¹⁰ Finally, amitrip-

tyline is an effective antagonist in animal models of NMDA-mediated neuronal plasticity. Like NMDA receptor antagonists, amitriptyline (30 μM) blocks evoked potentials and induction, but not maintenance of long-term potentiation in hippocampal slices.¹¹

Others have argued that it is not surprising that tricyclic antidepressants possess NMDA receptor antagonist properties, given their structural similarity to classical NMDA receptor antagonists such as MK-801.²² Indeed, traditional NMDA receptor antagonists are active in animal models of depression, and some believe it is this property, rather than monoamine reuptake inhibition, that is responsible for the antidepressant activity of amitriptyline and related compounds.²³

N-Methyl-D-Aspartate Receptor Activation in Hyperalgesia

Central sensitization leading to hyperalgesia and allodynia could occur *via* increased excitability in the dorsal horn, decreased inhibition, and/or structural reorganization.²⁴ Evidence for each of these mechanisms exists; however, most recent work has focused on increased excitability, and has repeatedly demonstrated the pivotal role of excitatory amino acids acting at NMDA receptors in producing sensitization. For example, brief, low-frequency C-fiber stimuli lasting tens

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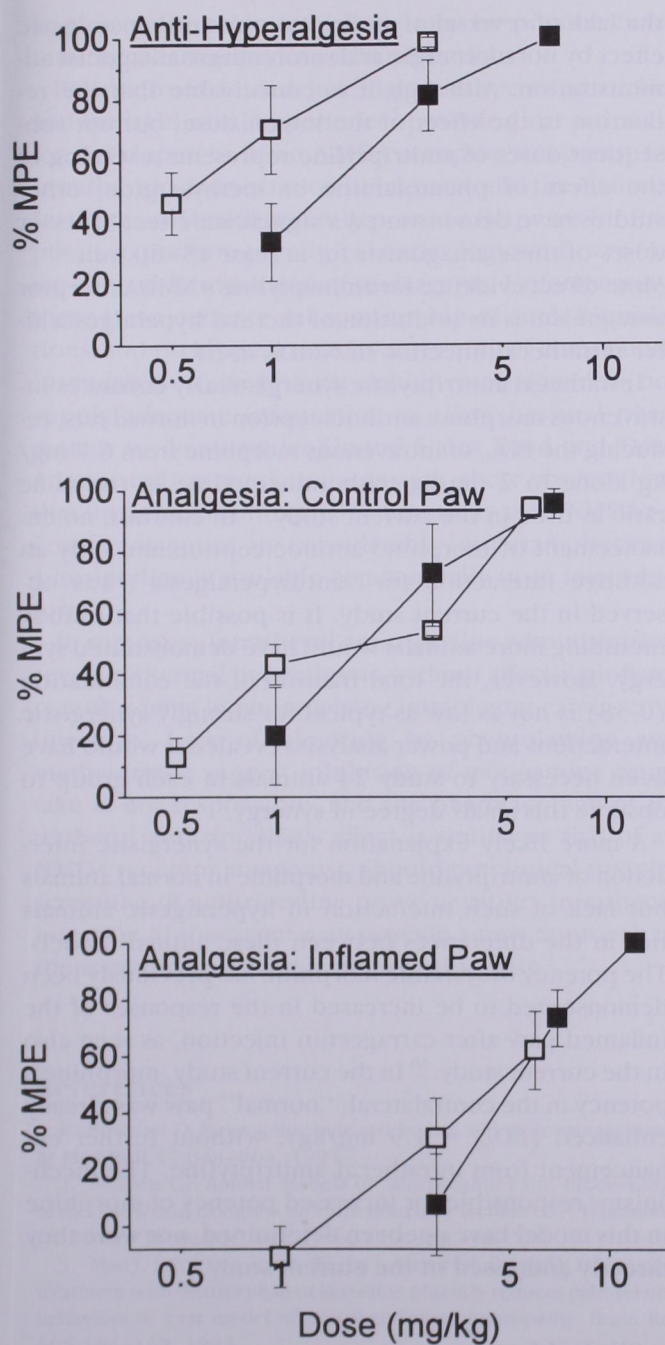


Fig. 4. Percent maximal possible antinociceptive effect after intravenous injection of morphine alone (■) or in fixed ratio combination with intrathecal injection of amitriptyline 10:1000 (□) 3 hr after intraplantar carrageenin injection. Upper panel demonstrates the dose-dependent return of decreased withdrawal latency after intraplantar carrageenin injection to precarrageenin injection values. Other panels demonstrate the dose-dependent increase in withdrawal latency from precarrageenin values to cutoff in noninjected, control paw (middle panel) or carrageenin-injected paw (lower panel). Each value represents the mean \pm SEM of six animals.

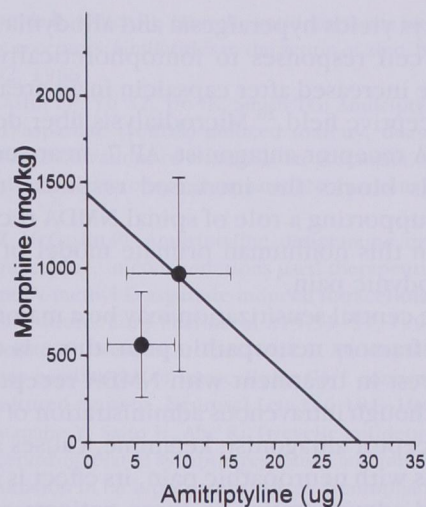


Fig. 5. Isobologram depicting the interaction between intravenous morphine and intrathecal amitriptyline injection in increasing withdrawal latency after intraplantar carrageenin injection to precarrageenin baseline. The observed point and theoretical additive point are depicted with 95% confidence intervals. Points do not differ by Student's *t* test.

of seconds can produce a central facilitation ("windup") lasting several hundred-fold longer, associated with expansion of receptive field size, decrease in firing threshold, and increase in responsiveness (see ²⁴). Microiontophoretic or intrathecal injection of specific NMDA receptor antagonists block these effects in animals.²⁵ Similarly, intradermal capsaicin injection

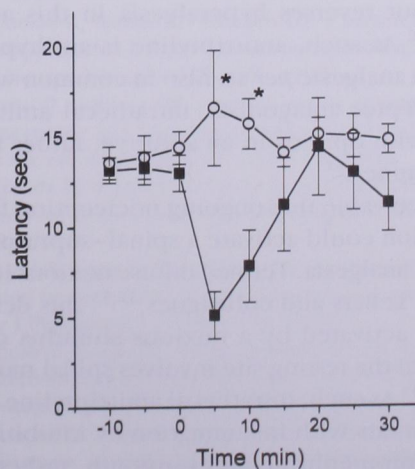


Fig. 6. Withdrawal latency before, and after intrathecal injection at time 0 of 1 μ g N-methyl-D-aspartate, in animals pretreated with intrathecal injection of saline (■) or 60 μ g amitriptyline (○). Each symbol represents the mean \pm SEM of six animals. **P* < 0.05 versus saline pretreatment.

in monkeys yields hyperalgesia and allodynia, and dorsal horn cell responses to iontophoretically applied NMDA are increased after capsaicin in an area adjacent to the receptive field.²⁶ Microdialysis fiber delivery of the NMDA receptor antagonist, AP-7, near such dorsal horn cells blocks the increased response to tactile stimuli, supporting a role of spinal NMDA receptor activation in this nonhuman primate model of hyperalgesic/allodynic pain.⁴

Because central sensitization may be a major contributor to refractory neuropathic pain, there is considerable interest in treatment with NMDA receptor antagonists. Although intravenous administration of the weak NMDA receptor antagonist, ketamine, causes analgesia in patients with neuropathic pain, its effect is brief and prolonged administration in these patients causes intolerable cognitive effects.²⁷ Because intrathecal administration of NMDA receptor antagonists produces a more profound antihyperalgesic effect than systemic administration²⁸ it would be more logical to administer these drugs by this route. As such, intrathecal administration of the receptor NMDA antagonist, 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), has recently been demonstrated to reverse hyperalgesia and allodynia in a patient with long-standing neuropathic pain.⁵

The current study strongly supports an NMDA receptor antagonist property of intrathecal amitriptyline being responsible for its reversal of hyperalgesia. In common with other NMDA receptor antagonists,²⁹ intrathecal amitriptyline injection has no effect in normal animals, but reverses hyperalgesia in this and other models.^{2,30} As such, amitriptyline is antihyperalgesic rather than analgesic *per se*. Also in common with other NMDA receptor antagonists, intrathecal amitriptyline interacts with opioids in an additive, rather than synergistic manner.³¹

It is conceivable that ongoing nociception from paw inflammation could activate a spinal-supraspinal-spinal loop of analgesia. Termed diffuse noxious inhibitory control by LeBars and colleagues,^{32,33} this descending inhibition activated by a noxious stimulus delivered distant from the testing site involves spinal monoamine release.^{34,35} As such, intrathecal amitriptyline could be effective in rats with inflammation by inhibiting reuptake of norepinephrine and serotonin, rather than by NMDA receptor antagonism. Against this possibility, however, are the lack of analgesic effect of intrathecal amitriptyline on the contralateral paw, the additive rather than synergistic interaction with morphine, and

the lack of reversal of amitriptyline's antihyperalgesic effect by noradrenergic and serotonergic antagonist administration. Although it is conceivable that the reduction in the effect of the lowest dose, but not subsequent doses of amitriptyline represents a waning of the effect of phentolamine or methysergide, other studies have demonstrated a significant effect of lesser doses of these antagonists for at least 45–60 min.^{36–38} More direct evidence for amitriptyline's NMDA receptor antagonism is its inhibition of thermal hyperalgesia after intrathecal injection of NMDA itself.

Intrathecal amitriptyline synergistically enhances intravenous morphine antinociception in normal rats, reducing the ED₅₀ of intravenous morphine from 6.7 mg/kg alone to 2 mg/kg with amitriptyline in the same ratio as used in the current study.³⁹ In contrast, no enhancement of morphine antinociception and only an additive interaction for "antihyperalgesia" was observed in the current study. It is possible that a study including more animals would have demonstrated synergy. However, the total fraction of the combination (0.58) is not as low as typical for strongly synergistic interactions and power analysis revealed it would have been necessary to study 24 animals in each group to observe this small degree of synergy.

A more likely explanation for the synergistic interaction of amitriptyline and morphine in normal animals but lack of such interaction in hyperalgesic animals lies in the differences between these animal models. The potency of systemic morphine has previously been demonstrated to be increased in the responses of the inflamed paw after carrageenin injection, as seen also in the current study.⁴⁰ In the current study, morphine's potency in the contralateral, "normal" paw was already enhanced (ED₅₀ = 1.9 mg/kg), without further enhancement from intrathecal amitriptyline. The mechanisms responsible for increased potency of morphine in this model have not been determined, nor were they directly addressed in the current study.

Clinical Implications

Systemic amitriptyline diminishes, but does not abolish hyperalgesia or ongoing pain behavior in animal models of inflammatory or neuropathic pain (formalin injection,⁴¹ sciatic nerve ligature,⁴² peripheral deafferentation,^{43,44} rhizotomy,⁴⁵ diabetic neuropathy⁴⁶). Similarly, systemic amitriptyline exhibits modest efficacy in humans with chronic pain,^{47,48} postherpetic neuralgia,⁴⁸ and diabetic neuropathy.⁴⁹ These results

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suggest more profound effects may be possible with intrathecal amitriptyline administration.

Results from animal investigations reviewed earlier and initial clinical experience⁵ provide clear rationale for development of an NMDA receptor antagonist for intrathecal administration in humans, and the National Institutes of Health recently posted a Request for Proposals to perform preclinical toxicology studies to foster clinical introduction of such agents. Unfortunately, there is no commercial sponsorship of such formulations, and preclinical toxicity screening of compounds formulated on site by individual investigators does not supply adequate information to allow hospital pharmacies to do so under United States Food and Drug Administration regulations. As such, these observations that intrathecal amitriptyline functions as an NMDA receptor antagonist are considerably important, because amitriptyline is available commercially in an injectable form.

In summary, intrathecal amitriptyline administration reverses thermal hyperalgesia without affecting inflammatory edema in rats receiving intraplantar carrageenin injection. Lack of blockade by phentolamine and methysergide suggest inhibition of monoamine reuptake is not responsible, and the pharmacology of intrathecal amitriptyline's effect is similar to that of an NMDA receptor antagonist. Should preclinical toxicity screening of amitriptyline prove negative, intrathecal injection of this agent may provide a new approach to the treatment of chronic neuropathic pain.

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