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AMPA/Kainate Antagonist LY293558 Reduces Capsaicin-evoked Hyperalgesia but Not Pain in Normal Skin in Humans

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Background: **Animal studies suggest that α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid–kainate (AMPA–KA) receptors are involved in pain processing. The effects of the competitive AMPA–KA antagonist LY293558 in two types of experimental pain in human volunteers, brief pain sensations in normal skin, and mechanical allodynia–pinprick hyperalgesia were studied after the injection of intradermal capsaicin.**

Methods: **Brief intravenous infusions of the competitive AMPA–KA antagonist LY293558 were given to 25 healthy volunteers to examine acute toxicity and analgesic effects. Fifteen volunteers then entered a double-blinded, three-period crossover study. In a Phase II study, LY293558 infusions (100% maximally tolerated dose *vs.* 33% maximally tolerated dose *vs.* placebo) began 10 min after intradermal injection of 250 μg capsaicin in volar forearm. Spontaneous pain, areas of mechanical allodynia and pinprick hyperalgesia, and side effects were determined every 5 min for 60 min.**

Results: **The median maximally tolerated dose was 1.3 ± 0.4 (range, 0.9–2.0) mg/kg. Tests of cognitive and neurological function were unchanged. Dose-limiting side effects were hazy vision in 95% of volunteers and sedation in 40%. There were no significant changes in electrical or warm–cool detection and pain thresholds or heat pain thresholds. LY293558 had little effect on brief pain sensations in normal skin. Both high and low doses of LY293558 significantly reduced pain intensity, pain unpleasantness, and the area in which light brush evoked pain after intradermal capsaicin. There was a trend toward a dose–response effect of LY293558 on the area in which pinprick evoked pain after intradermal capsaicin, which did not reach statistical significance.**

Conclusions: **The authors infer that AMPA–KA receptor blockade reduces the spinal neuron sensitization that mediates capsaicin-evoked pain and allodynia. The low incidence of side effects at effective doses of LY293558 suggests that this class of drugs may prove to be useful in clinical pain states. (Key words: Allodynia; glutamate; nociception; sensory testing.)**

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THE frequent failure of conventional analgesics to provide complete pain relief has spurred the search for more powerful interventions.[1] Anatomical,[2,3] electrophysiological,[4–6] and behavioral studies[7,8] suggest that glutamate is one of the most important transmitters of excitation between the primary afferent and spinal neurons involved in pain processing, and that antagonists of glutamate receptors therefore might be useful analgesics. The major drawback in this therapeutic strategy is the ubiquity of glutamate in central nervous system function. This has become apparent in studies of N-methyl-D-aspartate receptor antagonists: Although administra-

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tion of these drugs to humans reduces many types of acute and chronic pain,[9-12] adverse reactions including sedation, dysphoria, catatonia, and sensory distortions limit doses to those providing only modest degrees of pain relief. Furthermore, N-methyl-D-aspartate antagonists reduce only certain components of pain in animal and human studies,[13,14] suggesting that non–N-methyl-D-aspartate glutamate receptors or other transmitter systems may play important roles. Animal studies of specific agonists and antagonists suggest a role in pain processing for the other two classes of glutamate receptors, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid-kainate (AMPA–KA)[15,16] and metabotropic receptors,[17] but their analgesic effects have been less intensively studied than those of N-methyl-D-aspartate antagonists, and there are no human studies.

Receptors for AMPA (GluR1-4) are found throughout all superficial laminae of the dorsal horn pre- and postsynaptically,[2,18] and AMPA agonists enhance responses of spinal neurons to noxious and non-noxious stimuli.[19] Kainate receptors (Glu 5-7; KA2) are expressed diffusely in the dorsal horn, mostly in lamina II.[2,18] The results of behavioral studies of the analgesic effects of AMPA–KA receptor antagonists appear to conflict. Hunter and Singh[20] reported that intrathecal NBQX blocked the first phase of the excitatory response to rat paw formalin injection, which is thought to be a model of processing of acute noxious stimulation in previously normal tissue, but it had little effect on the second phase of the response, which reflects the development of sensitization of sensory neurons 30 min or more after injury. Simmons *et al.*[21] used a different drug, the competitive AMPA–KA antagonist LY293558,[22-24] and found exactly the opposite effect, reduction of the second phase but not the first phase of the formalin response.

We designed a human study of brief systemic infusions of LY293558 to address two questions:

1. Do AMPA–KA receptor antagonists have analgesic effects in humans, and if so, which types of pain are most affected? Using a battery of well-studied experimental pain stimuli, we addressed two different types of pain processing. First, acute pain processing in the baseline state of the nervous system was assessed by applying brief thermal and electrical stimuli to normal skin. Second, the contribution of sensitization of spinal pain-processing neurons was assessed using the intradermal capsaicin model of hyperalgesia. Animal and human experiments have shown that injection of capsaicin causes an intense barrage of impulses from C nociceptors, which sensitizes spinal neurons, temporarily producing areas of hypersensitivity to mechanical stimuli, termed allodynia (pain induced by a stimulus that is not normally painful, such as light brushing) or hyperalgesia (increased pain reported after a stimulus that is normally painful).[10,25-27] There is evidence for sensitization of central neurons in pain caused by burn,[28] trauma,[29] nerve injury,[30] visceral disease,[31] arthritis,[32] and many other clinical conditions.
2. Can analgesic effects be detected at doses that do not interfere with alertness, cognition, mood, motor function, or sensory modalities mediated in part by glutamate receptors?

Materials and Methods

We studied medication-free healthy male volunteers (aged 21–47 yr). Studies were performed with informed consent and approval by the NIH/NIDR Institutional Review Board. The volunteers were unaware of the study's hypothesis and were required to turn away their gaze during stimulation.

LY293558 ((3s,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl) ethyl]dacahydoisoquinolone-3-carboxylic acid monohydrate; Lilly Research Laboratories, Indianapolis, IN) was reconstituted with 0.9% normal saline to a concentration of 10 mg/ml. Each single-dose infusion was administered over 15 min after dilution to 15 ml 0.9% normal saline.

Phase I Study

A preliminary dose-finding study (n = 6) was performed to determine the maximally tolerated dose (MTD) in six volunteers. The MTD was defined as that dose that produces a symptom or sign most likely a result of central nervous system dysfunction or any symptom that was persistent and troubling to the participant. The initial dose for participant 1 was 0.01 mg/kg, and each subsequent dose was at most twice the highest previously administered dose. During each session, we evaluated neurologic function, cognitive function, and side effects at baseline and every 15 min for 60 min. A simple neurologic examination involved checking for nystagmus (tested by observing the volunteer's eyes during lateral gaze) and ataxia (tested by observing the volunteer when he moved his pointed finger to the examiner's finger and back to his own nose). Cognitive function was assessed using the Digit Symbol Substitution Test.[33] Subjective side effects were determined us-

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ing a 100-mm visual analog scale to assess the presence of visual changes and sedation.

After the initial dose-finding study in six volunteers, we administered escalating doses of LY293558 to 16 additional participants to determine the MTD for each of them, the dose to be used in the placebo-controlled trial. Each dose was no greater than 33% higher than the previous dose. Procedures during each session were identical to those of the preliminary dose-finding study. Twenty volunteers achieved their MTD.

In the volunteer who received the highest dose in the preliminary dose-finding study, visual evoked potentials were elicited by contrast reversal of a checkerboard pattern (check sizes 15, 30, and 60 mm). Electroretinography (Ganzfeld Flash ERG) were used to demonstrate rod- and cone-mediated responses after dark-adaptation.

Effect of LY293558 on Brief Nociceptive Stimuli

We determined the effect of LY293558 on painful and nonpainful sensations in normal skin by evaluating brief stimuli every 15 min for 60 min during 87 dose sessions in 25 volunteers.

Electrical Detection and Pain Thresholds. Monopolar constant-current rectangular pulses were delivered at 0.5 Hz through bipolar 7-mm diameter electrodes spaced 23 mm apart (center to center) on the volar forearm, applied along the axis of the limb with the cathode directed proximally. The volunteers were seated with their arms resting outward and supinated, and electrodes were applied at the level of the heart. To avoid stimulation of nociceptors at suprathreshold intensities, an ascending series of stimulus intensities was delivered in 0.01-mA steps to each site, starting at zero and gradually increasing in increments of 0.01 to 0.05 mA until a sensation was evoked (detection threshold) and further increased until the sensation changed to definite pain (pain threshold).

Warm–Cool Detection and Heat–Cold Pain Thresholds. Pain and detection thresholds to warm and cool stimuli were determined with a 4×4 cm^2 Peltier probe, whose temperature changed at a rate of 1°C/s from a baseline of 33°C.

Pain Intensity and Unpleasantness of 2-s Stimuli at 1°C, 2°C, and 3°C above the Predrug Heat Pain Threshold. The volunteers rated pain intensity and unpleasantness of 3-s heat stimuli at fixed temperatures of 1°C, 2°C, and 3°C above the pain threshold determined at baseline. Pain intensity and unpleasantness were recorded by choosing from a list of 13 words, which are assigned values based on ratio scales.[34] Sensitivity of the scale in distinguishing between active and control treatment groups has been demonstrated for experimental and clinical pain states.[35]

Phase II Study: Effect of LY293558 on Capsaicin-evoked Pain

To determine the effect of two doses of LY293558 (33% *vs.* 100% MTD *vs.* placebo) on pain and mechanical hyperalgesia after intradermal capsaicin,[36] 15 volunteers completed a three-period double-blinded crossover study. In each session, we injected 250 μg intradermal capsaicin in the volar forearm. Capsaicin (8-methyl N-vanillyl-6-nonenamide) was obtained from Fluka (Ronkonkoma, NY) and dissolved in 15% Tween 80 at a concentration of 10 mg/ml. The 15-min LY293558 infusion began 10 min after the capsaicin injection. Spontaneous pain, areas of mechanical allodynia and pinprick hyperalgesia, and side effects were determined every 5 min for 60 min. Brush allodynia was mapped by stroking the skin with a #2 flat Princeton watercolor brush at standard pressure (bending the distal 2 mm of the brush) and at a rate of 1 cm/s. Pinprick hyperalgesia was mapped using a standard safety pin that was pressed against the skin until dimpling was visible. The skin temperature was fixed at 36°C by a radiant heat lamp. After the experiment, the points defining areas of allodynia and pinprick hyperalgesia were connected. The resulting polygons were scanned (Adobe Photoshop 4.0, Adobe Systems, Inc., San Jose, CA) and areas calculated (NIH Image 1.1, developed at the National Institutes of Health, Bethesda, MD).

To determine whether the volunteers could guess what treatment they received, we administered blinding questionnaires after each session was complete.

Statistical Analysis

Our main outcome variables were spontaneous pain intensity, allodynia, and hyperalgesia over 60 min. We used the outcome of spontaneous pain intensity[34] from 10 to 60 min after capsaicin to determine the sample size for this trial. Assuming a type I error of 0.05, a type II error of 0.2, and a within-subject standard deviation of 1.7 (RH Gracely *et al.*, unpublished data), we would detect a difference of 1.2 units on the Gracely scale with >80% power, provided that our sample size is at least 15. A reduction of 1.2 units on the Gracely scale (its maximum value of 1.77 corresponds to "very intense") corresponds to a reduction in pain from "very intense" to "weak."

Each time point was normalized to the baseline value.

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Table 1. Dose-limiting Toxicity of LY293558 (n = 20)

Dose (mg/kg)	New SE	Cumulative SE	New Side Effects at Each Dose		
			Vision Change	Sedation	Headache
0	0	0	0	0	0
0.9	5	5	4	2	0
1.0	1	6	1	0	0
1.2	3	9	3	2	0
1.3	2	11	2	1	0
1.5	2	13	2	0	0
1.6	2	15	2	2	0
1.8	4	19	4	1	2
2.0	1	20	1	0	0

Values are the number of subjects experiencing side effects at each dose level. The severity of drug effects was rated as mild at each dose level. In all cases, a quantitative paper and pencil test (Digit Symbol Substitution Test) was unchanged from baseline.

For pain intensity or unpleasantness, the baseline was defined as the highest value in the 30 s after the capsaicin injection; for areas of allodynia or hyperalgesia, the baseline was defined as the observation at 5 min after capsaicin injection. The paired Student's *t* test was used to examine the mean of the paired differences of each treatment to placebo from 10 to 60 min after capsaicin.

Results

Toxicity

The first volunteer to experience side effects (subject A) remained alert with normal results of the neurologic examination and cognitive function, but he noted blurred vision about 15 min after the start of the study drug infusion (dose = 1.8 mg/kg), which he described as white clouds in the periphery, sparing central vision. At 35 min, the cloudiness spread centrally to involve all fields. Symptoms resolved in 60 min. Then we reevaluated all previous drug infusions and, in retrospect, noted that the three other volunteers who received the three other highest doses (all >1 mg/kg) also reported transient and mild white visual obscurations. These four volunteers were evaluated using electrophysiologic tests 2 days to 2 weeks after symptoms resolved. Visual evoked responses showed good reproducibility. All visual evoked potentials showed a main positive peak (P100) recorded at the mid-occipital electrode with normal latency, with amplitudes in the low normal range. Electroretinography (Ganzfeld Flash ERG) demonstrated that rod- and cone-mediated responses recorded after dark adaptation were normal in amplitude and implicit time (latency to peak). The maximal retinal responses showed normal amplitude and implicit time. Oscillatory potentials were normal. Cone-mediated responses recorded after light adaptation were normal in amplitude and implicit time. There were no interocular differences for either test.

Normal serial electroretinogram, visual evoked response, and visual fields in the presence of subjective visual changes suggested that there were no permanent adverse effects of LY293558 on retinal or cortical function or on conduction along the central visual pathways. Subject A underwent electrophysiological recordings and visual field testing during two repeated infusions at MTD; again, all results were normal.

Seventy-eight infusions were administered to 20 volunteers (including four from the preliminary study) at nine dose levels (table 1). The median MTD was 1.3 ± 0.4 (range, 0.9–2.0) mg/kg. In every volunteer, tests of cognitive and neurologic function remained unchanged from baseline, even at MTD. Subjective side effects were mild and again included visual symptoms described as "looking through a haze," "like being in the shower looking through steam," "white clouds," "white smoke," "like fog filling the room" (described by 19 of 20 [95%] volunteers; onset, 17 ± 5 min; duration, 36 ± 19 min), sedation (8 of 20 [40%]; onset, 29 ± 30 min; duration, 46 ± 67 min), and bifrontal headache (2 of 20 [10%]; onset, 110 ± 99 min; duration, 20 ± 14 min).

Effect of LY293558 on Brief Nociceptive Stimuli

There were no significant changes in electrical or warm–cool detection and pain thresholds (data not shown). Suprathreshold heat pain intensity was not significantly reduced for 60 min after LY293558 infusions as compared with baseline, although a nonsignificant trend toward reduction of pain intensity after the higher-dose infusions was noted (repeated measures analysis of variance; dose × time interaction; $P = 0.11$; fig. 1).

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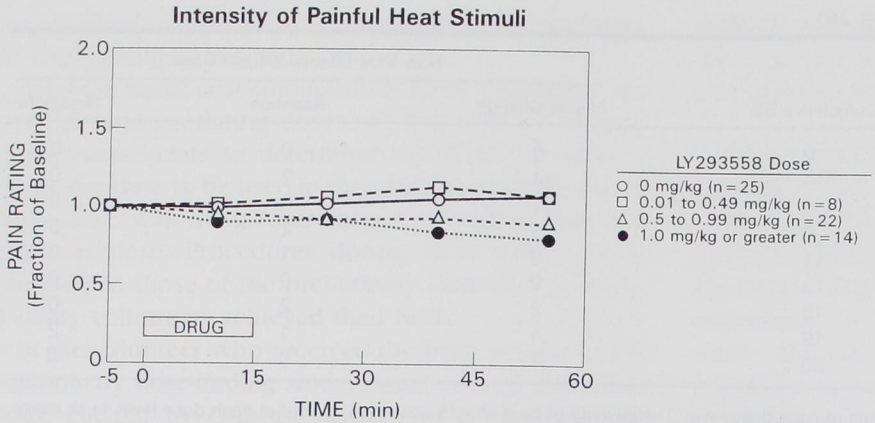

Fig. 1. Intensity of suprathreshold painful heat stimuli delivered to normal skin. One-second thermal stimuli at a temperature 3°C above the predrug pain threshold were administered to the volar forearm before and during 87 infusions in 25 volunteers. Spontaneous pain intensity is plotted as a percentage of baseline. A trend toward reduction of pain intensity after the higher-dose infusions was not statistically significant.

Effect of LY293558 on Capsaicin-evoked Pain

For both the 33%MTD and 100%MTD groups, spontaneous pain intensity (fig. 2A: $P = 0.004$ and 0.007 for 33%MTD and 100%MTD, respectively) and unpleasantness (fig. 2B: $P = 0.003$ and 0.037), and areas of allodynia (fig. 3A: $P = 0.017$ and 0.002) were significantly less in volun-

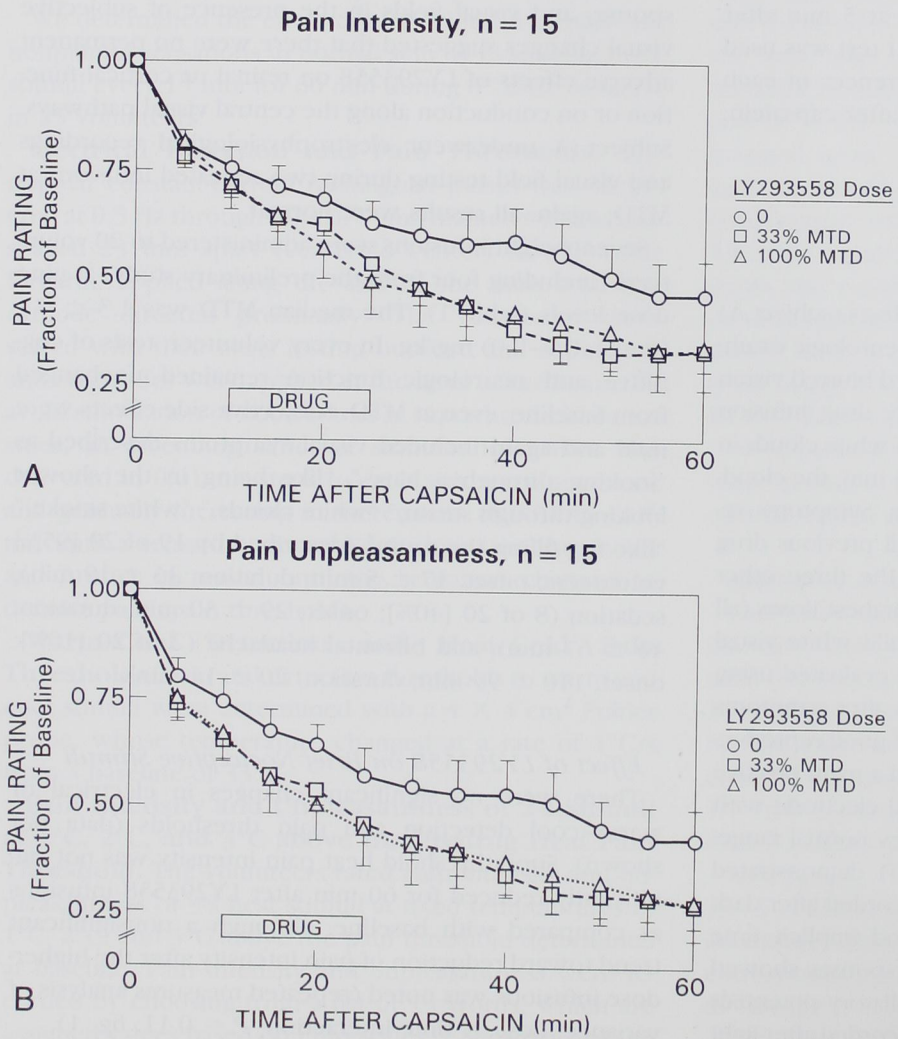

Fig. 2. Capsaicin-evoked spontaneous pain intensity and unpleasantness. Spontaneous pain intensity (*A*) and unpleasantness (*B*) are plotted as percentages of baseline, defined as the peak score immediately after injection of intradermal capsaicin. The mean pain intensity from 10 to 60 min after the capsaicin dose was significantly less for both 33%MTD and 100%MTD compared with saline infusion.

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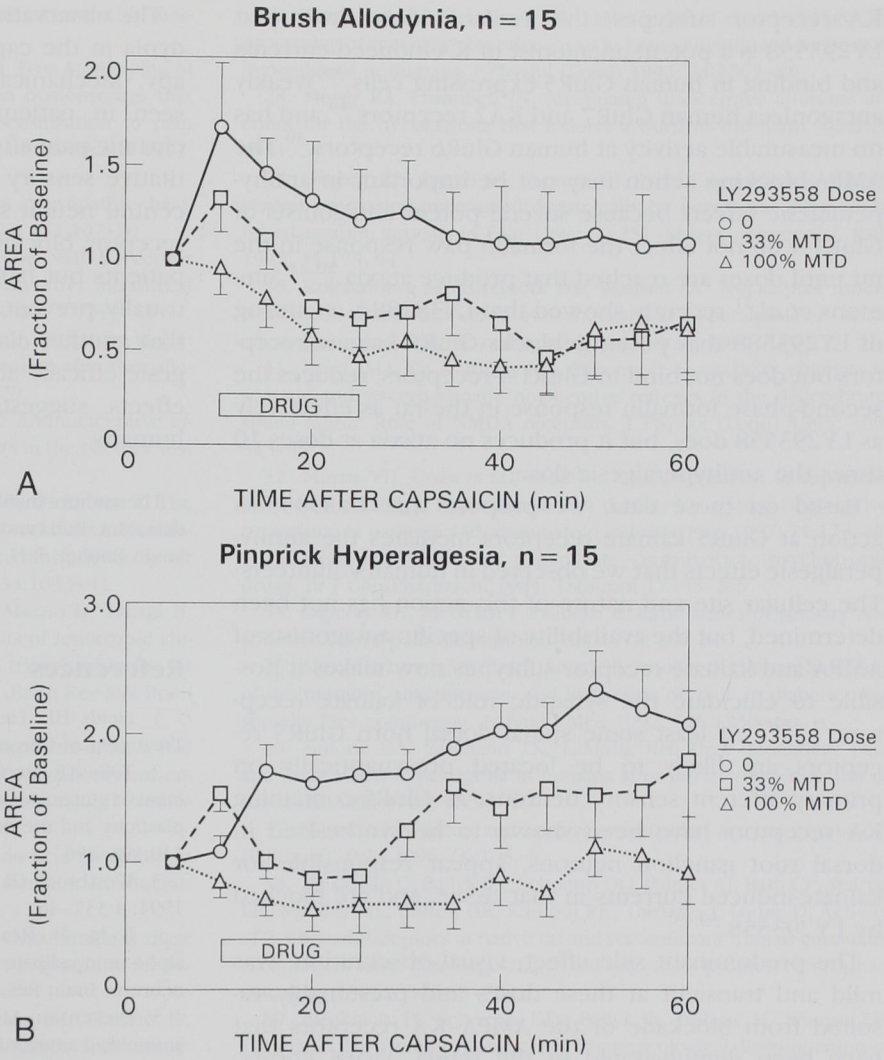

Fig. 3. Capsaicin-evoked allodynia and hyperalgesia. Areas of (*A*) allodynia and (*B*) hyperalgesia are plotted as percentages of baseline, defined as the area determined 5 min after injection of intradermal capsaicin. Mean areas of allodynia from 10 to 60 min after capsaicin were significantly less for both 33%MTD and 100%MTD. A trend toward a reduction of the area of pinprick hyperalgesia was not statistically significant. Mapping of allodynia and pinprick hyperalgesia at each time point began at the time indicated and took 1 or 2 min. Therefore, the 10-min point, which already shows the effects of the drug infusion begun at 10 min, indicates that the drug already has some effect within 2 min of starting LY293558.

teers who received LY293558 rather than placebo. Areas of pinprick hyperalgesia were less in the 33%MTD and 100%MTD groups than placebo, although these effects were not significant (fig. 3B: $P = 0.38$ and 0.05).

Nine of 15 volunteers (60%) were able to correctly guess during which of the three treatment periods they received 100%MTD; 5 of 15 (33%) were able to correctly guess during which treatment period they received 33%MTD, a finding no better than chance, indicating that the analgesic and antiallodynic effects noted with the 33%MTD were not influenced by volunteers' ability to identify which treatment they had received.

Discussion

To our knowledge, this is the first report of the effects of AMPA-KA antagonists in humans. Our data show that AMPA-KA receptors play a role in pain transmission in humans: LY293558 significantly decreased both spontaneous pain and the spread of mechanical hyperalgesia evoked by intradermal capsaicin but did not significantly reduce brief suprathreshold pain sensations in normal skin. Based on the differential analgesic response between two human experimental models of pain, we infer that AMPA-KA receptors primarily contribute to the processes leading to sensitization of central neurons.[10,25-27,37]

An understanding of the AMPA-KA receptor subtypes mediating the relatively selective analgesic action of LY293558 in this study might facilitate the development of analgesic drugs with fewer side effects. LY293588 is a relatively potent antagonist at AMPA-type glutamate receptors (GluR1-4) and KA receptors.[38] With regard to

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KA receptor subtypes, the available data show that LY293558 is a potent antagonist of KA-induced currents and binding in human GluR5-expressing cells,[39] weakly antagonizes human GluR7 and KA2 receptors,[40] and has no measurable activity at human GluR6 receptors.[39] The AMPA-blocking action may not be important in antihyperalgesic effects because several potent antagonists of GluR1-4 do not affect the formalin paw response in the rat until doses are reached that produce ataxia.[20,21] Simmons *et al.*[21] recently showed that LY382884, an analog of LY293588 that potently blocks GluR5 kainate receptors but does not bind to GluR1-4 receptors, reduces the second-phase formalin response in the rat as effectively as LY293558 does, but it produces no ataxia at doses 10 times the antihyperalgesic dose.

Based on these data, we propose that LY293558's action at GluR5 kainate receptors mediates the antihyperalgesic effects that we observed in human volunteers. The cellular site and nature of this action has not been determined, but the availability of specific antagonists of AMPA and kainate receptor subtypes now makes it possible to elucidate the synaptic role of kainate receptors.[21,41,42] At least some spinal dorsal horn GluR5 receptors are likely to be located presynaptically on primary afferent sensory neurons, as GluR5-containing KA receptors have been shown to be synthesized in dorsal root ganglion neurons, appear responsible for kainate-induced currents in that tissue, and are blocked by LY293558.[39,43]

The predominant side effect, visual obscuration, was mild and transient at these doses and presumably resulted from blockade of the AMPA-KA receptors that have been demonstrated in the retina, visual cortex, lateral geniculate nucleus, superficial superior colliculus, and nucleus of the optic tract.[44,45] We are unaware of animal data to specify which AMPA-KA receptor subtypes mediate this effect. However, because the results of all the psychophysical and electrophysiologic tests were normal, we could not localize the effect of LY293558 within the visual system. In rats receiving 14-day infusions of daily 10 mg/kg intravenous boluses of LY293558, we noted no histopathologic changes in the optic tract, superior colliculus, or multiple areas of cortex, including the visual cortex (W. Jordan, unpublished data). Despite normal electrophysiologic recordings in subject A during peak LY293558 blood concentrations, the occurrence of visual effects in 19 of 20 volunteers suggests that close attention should be paid to the visual system during the preclinical and clinical development of AMPA-KA antagonists.

The observation that LY293558 reduces pain and allodynia in the capsaicin model has implications for therapy. Mechanical allodynia and hyperalgesia are often seen in patients with acute pain after surgery and chronic pain after nerve or soft tissue injuries, and quantitative sensory testing in many such patients suggests central neural sensitization.[12,29,30] N-methyl-D-aspartate receptor blockade has reduced pain in some of these patients but has been accompanied by side effects that usually prevent complete relief.[9,10-12] We have shown that another class of glutamate antagonists shows analgesic efficacy at doses that do not cause troubling side effects, suggesting promise for this class of drugs in humans.

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