Sequeira, Sandra and Jacques Näström. Low-affinity kainate in the superficial dorsal horn (Bonnot et al. 1996; Tölle et al. 1993), however, in contrast to NMDA and AMPA receptors, the role of kainate (KA) receptors in modulating their activity. In these neurons, coapplication of Glu and NMDA, as well as application of Glu immediately before NMDA, induced long- and short-lasting depressions of NMDA-induced currents as well as depression of NMDA-receptor–mediated excitatory postsynaptic currents. KA applied before NMDA mimicked Glu-induced attenuating effects. Furthermore, the low-affinity KA receptor antagonist 5-nitro-6,7,8,9-tetrahydrobenzo[G]indole-2,3-dione-3-oxime potentiated Glu-induced NMDA-receptor–mediated currents in neurons responding differentially to Glu and NMDA. These results provide evidence for a novel mechanism, which may relate to classical long-term depression, involving low-affinity KA receptors in long-lasting modulation of NMDA-receptor–mediated currents. This implies a physiological role of KA receptors in long-term modulation of sensory transmission in the superficial dorsal horn of rat spinal cord.

METHODS

Tissue preparation

The method employed for slice preparation of the rat spinal cord was modified from that described by Yoshimura and Nishi (1993). Briefly, 3- to 5-wk-old male Sprague-Dawley rats (B&K Universal AB, Sollientuna, Sweden) weight 80 ± 3 g (mean ± SE); ranging from 46 to 175 g (n = 134) were anesthetized with urethane (Cervero and Iggo 1980; Christensen and Perl 1970; Kumazawa and Perl 1978). Excitatory synaptic transmission, relayed from aδ and C fiber afferents to dorsal horn neurons, is mediated primarily by the excitatory amino acid (EAA) L-glutamate (Glu) acting at glutamate receptors (for reviews, see Marmo 1988; Watkins and Evans 1981). More recent studies have indicated that glutamate receptors of both N-methyl-D-aspartate (NMDA) and non-NMDA types also may underlie modulation of excitatory transmission, including long-term depression (LTD) (for reviews, see Asztely and Gustafsson 1996; Linden and Connor 1995).

NMDA and non-NMDA receptors of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type are expressed on many neurons of the spinal cord with the highest density of binding sites being found in the superficial dorsal horn (Aanonsen and Seybold 1989; Jakowec et al. 1995; Monaghan and Cotman 1985; Tölle et al. 1993). Kainate (KA) receptors encoding the low-affinity binding sites (GluR5–GluR7) (Bettler and Mulle 1995) are also abundant in the superficial dorsal horn (Bonnot et al. 1996; Tölle et al. 1993), however, in contrast to NMDA and AMPA receptors, the role of KA receptors in synaptic function remains largely unknown (for reviews, see Bettler and Mulle 1995; Lerma et al. 1997).

Recently KA was demonstrated to induce depression of NMDA-receptor–mediated synaptic currents (Chittajallu et al. 1996) that was suggested to result from action at presynaptic low-affinity KA receptors. Although this is a possibility, the mechanisms underlying such synaptic depression have yet to be fully elucidated.

Previous studies have demonstrated that a substantial proportion of superficial dorsal horn neurons are Glu-insensitive (Näström et al. 1994; Schneider and Perl 1985, 1988; Yajiri et al. 1997; Yoshimura and Jessell 1990). Furthermore, neurons in this region possess differential sensitivities to NMDA and Glu (Näström et al. 1994). We undertook to investigate the cellular mechanisms possibly underlying this differential responsiveness, paying attention to the part of KA receptors and physiological characteristics of those neurons exhibiting it.
Whole cell patch-clamp recordings

Whole cell patch-clamp recordings were made from SG neurons. Through a dissecting microscope, the SG was identified as a distinct, relatively translucent band across the dorsal horn. Patch pipettes (5–8 MΩ) were pulled from borosilicate glass (No. 7052, A-M Systems, Everett, WA), and pipette tips were coated with Sigmacote and filled with internal solution of the following composition (in mM): 130 K-glucuronate, 11 ethylene glycol-bis(β-aminoethoxy ether)-N,N,N’,N’-tetraacetic acid, 5 NaCl, 1 CaCl₂, 1 MgCl₂, 10 HEPEs, 2–4 Mg-ATP, 0.2 Li-GTP, and 0.005 phalloidin; osmolarity was 290–300 mOsm, pH was adjusted to 7.2 using KOH. The liquid junction potential was measured at ~9 mV by the method described by Neher (1992) and has been subtracted from all potential values given. Gigaohm seals of SG neurons were achieved using the blind technique, i.e., by monitoring current flow through the pipette on an oscilloscope while lowering the pipette onto a cell. Whole cell recordings were performed in voltage clamp mode at a holding potential of ~69 mV using a standard patch clamp amplifier (Axopatch 200A, Axon Instruments, Foster City, CA). Data were digitized and stored on video tape and computer expressed as a percent of the maximal NMDA-induced current for each cell. Normalized values were 100% of the mean NMDA-induced current for each cell. Normalized values were subsequently used to generate dose-response curves. Dose-response curves were obtained by plotting the mean ± SE values of the normalized currents against concentration. Any values deviating >2 SD from the mean were excluded from dose-response curves. On this basis, responses from one neuron were excluded. Dose-response curves were generated by fitting the data, by nonlinear regression, to the following equation:

\[ \text{Effect} = \frac{\text{Maximal effect}}{1 + \left( \frac{\text{EC}_{50}}{[D]} \right)^{z}} \]

where [D] represents the drug concentration, EC₅₀ represents the concentration that produces half-maximal effect, and z determines the slope and curvature. When appropriate, data were statistically analyzed by χ² test, Mann-Whitney U test, paired t-test, repeated measure analysis of variance (ANOVA) followed by Newman-Keuls post hoc test or Wilcoxon matched-pairs test, using Statistica version 5.0.

RESULTS

General characteristics of the sampled dorsal horn neurons

Stable tight-seal whole cell recordings were obtained from 137 superficial dorsal horn neurons, the visually located recording sites of which are illustrated in Fig. 1 (see figure legend for details). The average resting membrane potential was ~69 ± 0.3 (SE) mV (n = 134); ranging from ~54 to ~74 mV and the mean input resistance was 359 ± 17 MΩ (n = 137); ranging from 120 to 1,000 MΩ. These results are comparable with previous reports on dorsal horn neurons using similar recording techniques (Miller and Woolf 1996; Yajiri et al. 1997). Postsynaptic currents evoked by dorsal root stimulation were obtained from 107 neurons. Excitatory postsynaptic currents (EPSCs) were evoked in the majority of these neurons. On the basis of stimulus intensity and conduction velocity, a neuron was labeled A only if EPSCs were associated with activity in myelinated Aδ fibers (30–60 μA, 2–4 m/s). Neurons with EPSCs associated with activity in C fibers only, were classified as C only (120–300 μA, <1 m/s). Neurons with EPSCs associated with activity in myelinated A fibers and unmyelinated C fibers were classified as A + C. Based on these criteria, 73% (73/100) of the neurons were classified as A only, 11% (11/
100) were classified as C only and 16% (16/100) were classified as A + C. Inhibitory postsynaptic currents (IPSCs) were evoked by dorsal root stimulation in 17% (18/107) of the neurons.

Inward currents induced by Glu and NMDA

Given diffusion and inactivation considerations (see DISCUSSION), 12 mM Glu represents a relevant physiological concentration. Bath applications of 12 mM Glu induced inward currents of 358 ± 39 pA; ranging from 20 to 1,806 pA, in nearly all 105/110 (95%) of the neurons tested. The average duration of Glu-induced currents at 50% of peak inward current was 26 ± 1 s (n = 47). Bath application of NMDA (100 μM) induced inward currents of 828 ± 67 pA; ranging from 60 to 3,632 pA, in 112/116 (97%) of the neurons tested. The average duration of NMDA-induced currents at 50% of peak inward current was 73 ± 2 s (n = 47). In about one-half the cells, NMDA-receptor-mediated currents induced by Glu were significantly smaller in peak amplitude than those induced by NMDA (Fig. 2A). A comparison of a number of neurons at 12 mM Glu and 100 μM NMDA, concentrations giving maximal NMDA-receptor-mediated currents in the highly responsive neurons, showed a statistically significantly smaller peak amplitude for Glu-induced currents compared with maximal NMDA-induced currents (P < 0.001, Mann-Whitney U test; Fig. 2, B and C). NMDA and the major part of Glu-induced currents appear to be NMDA-receptor-mediated because they were blocked by the noncompetitive NMDA receptor antagonist MK-801 (50 μM; by 99 ± 0.3% and 78 ± 4%; n = 4 and 6, respectively; Fig. 3). Responses remaining to 12 mM Glu after NMDA receptor block were further reduced in a reversible manner by increasing the concentration of the competitive non-NMDA receptor antagonist, NBQX, from 10 to 20 μM (by a total of 82 ± 5%; n = 5).

Attenuation of NMDA-induced currents

Glutamate receptor desensitization has been suggested as a mechanism underlying the absence of Glu excitatory action (Yoshimura and Jessell 1990). To determine whether glutamate receptor desensitization accounts for the relatively small Glu-evoked currents we noted, Glu and NMDA were superfused simultaneously to examine possible desensitization effects of Glu on NMDA-induced currents. Coapplication of Glu (12 mM) and NMDA (100 μM) attenuated NMDA-induced currents (52 ± 7%; n = 4; Fig. 4A). Figure 4B illustrates a similar experiment in which Glu was applied immediately before NMDA. The average duration of Glu/NMDA current lasted 51 ± 4 s (n = 5) from peak to peak. In this case, NMDA-induced currents were statistically significantly attenuated by Glu (P < 0.05 1-way repeated measure ANOVA; n = 5). In two of these five neurons, NMDA-induced currents remained fully depressed for 5 and 15 min after Glu application. In the remaining three neurons, NMDA-induced currents partially recovered 5 min after Glu application and were completely reversed after 15 min. The time course of these long- and short-lasting depressions (LLD and SLD) relate in time to what has previously been referred to as long- and short-term depression (LTD and STD) (Pockett 1995; Weisskopf et al. 1993). The pooled average depressions compared with the control NMDA-induced current were 53 ± 14% (P < 0.05 Newman-Keuls post hoc test), 48 ± 15% (P < 0.05 Newman-Keuls post hoc test), and 23 ± 22% at 0, 5, and 15 min, respectively. These findings are in contrast to individual Glu and NMDA applications in alternating order at 5-min intervals for up to a total of six agonist applications, where peak current amplitudes for Glu remained unchanged (P > 0.01 1-way repeated measure ANOVA; n = 8) and where NMDA-induced currents decreased only slightly, but still statistically significantly, after a third NMDA application (P < 0.01 1-way repeated measure ANOVA; n = 5) compared with the initial NMDA-receptor-mediated currents (i.e., virtually no rundown of NMDA-induced currents were noted during a 25-min period during control conditions). The average Glu-induced currents were 102 ± 13% (2nd application; n = 8) and 100 ± 16% (3rd application; n = 8) of the initial current. The average NMDA-induced currents were 97 ± 2% (2nd
receptor–mediated EPSCs after Glu/NMDA or KA/NMDA application correlate closely in magnitude and time course with changes in bath applied NMDA-induced currents ($r = 0.98; P < 0.05; n = 4$).

**Potentiating effects on Glu-induced currents by low-affinity KA receptor antagonist**

The action of a novel KA receptor antagonist, NS-102, on Glu-induced currents in Ca²⁺-free ACSF was examined for two reasons: first, to determine whether the small Glu-evoked currents observed in some cells are related to Glu’s application; $n = 5$) and 87 ± 3% (3rd application; $P < 0.01$ Newman-Keuls post hoc test; $n = 5$) of the initial current.

**KA-induced depression of NMDA currents**

Glu acts as a mixed agonist for all classes of EAA receptors (Watkins and Evans 1981). To elucidate the glutamate receptor class involved in the Glu inhibitory effects on NMDA receptors, we tested the actions of KA on NMDA-induced currents. KA (100 μM) applied immediately before NMDA evoked small inward currents by itself (29 ± 6 pA; $n = 7$) and significantly suppressed NMDA-induced currents ($P < 0.01$ 1-way repeated measure ANOVA; $n = 7$; Fig. 4C). In five of these seven neurons, KA induced a LLD of NMDA-induced currents. In the remaining two neurons, KA induced a SLD of NMDA currents that began 5 min after KA application and reversed completely after 15 min (e.g., Fig. 5B). The pooled average depression compared with the control NMDA-induced current were 24 ± 14% ($P < 0.05$ Newman-Keuls post hoc test), 45 ± 11% ($P < 0.01$ Newman-Keuls post hoc test), and 39 ± 15% ($P < 0.01$ Newman-Keuls post hoc test) at 0, 5, and 15 min, respectively.

**Attenuation of NMDA-receptor–mediated synaptic currents**

Bath application of agonist can affect synaptic as well as extrasynaptic receptors. To verify that the present in vitro model has implications for synaptic transmission, we examined Glu and KA depressing effects on NMDA-receptor–mediated EPSCs evoked by dorsal root stimulation. Application of Glu or KA immediately before NMDA application attenuated dorsal root-evoked EPSCs (by 64 ± 17%; Fig. 5A) in three of four neurons when AMPA receptors were blocked by NBQX. As shown in Fig. 5, changes in NMDA-

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**FIG. 3.** Noncompetitive NMDA receptor antagonist (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten,10 imine (MK-801; 50 μM) blocked NMDA (100 μM)-induced current (A) and Glu (12 mM)-induced current (B) in the presence of TTX (1 μM) and NBQX (10 μM). MK-801 was superfused for ≥10 min before agonist application (right). Agonists were superfused for a duration of 30 s, represented by black bar. Downward deflection of the curve reflects an inward current. Dashed line represents amplitude of control current. All traces are single sweeps.

**FIG. 4.** Glu- and kainate (KA)-induced depression of NMDA-receptor–mediated currents. **A:** responses evoked by Glu (12 mM), NMDA (100 μM), and Glu coapplied with NMDA. Note the reduction in amplitude of the current evoked by coapplication of Glu and NMDA. Calibration bar applies to all panels. **B:** top: control traces for Glu (12 mM) and NMDA (100 μM). Bottom: Glu-induced attenuating effects when Glu was applied immediately before NMDA application. Depression of NMDA-induced currents were studied 5 and 15 min after Glu/NMDA double application. All traces are from the same neuron. Calibration bar applies to all panels. Note long-lasting attenuation of NMDA-induced currents. **C:** top: control traces for Glu (12 mM) and NMDA (100 μM). Bottom: KA-induced attenuating effects when KA (100 μM) was applied directly before NMDA application. Depression of NMDA-induced currents were recorded 5 and 15 min after KA/NMDA double application. All traces are from the same neuron. Calibration bars applies to all panels. Note long-lasting depression (LLD) of NMDA currents indicating a KA-induced LLD of NMDA-mediated responses. Agonists were superfused for a duration of 30 s, represented by black bar. Dashed line represents amplitude of control current. ACSF contained 10 μM NBQX and 1 μM TTX in all experiments (A–C).
own inhibitory action on Glu-induced NMDA receptor-mediated currents and second, to determine whether these receptors are located pre- or postsynaptically. As shown in Fig. 6, maximal Glu (12 mM)-evoked currents in the presence of NS-102 (10 μM), were significantly augmented (by 157 ± 33%; P < 0.01 Wilcoxon matched pairs test; n = 11) relative to control amplitudes in Ca²⁺-free ACSF. In 2 of these 11 neurons, NS-102 enhanced Glu (12 mM)-induced currents to a peak amplitude similar (97 ± 1%) to those produced by NMDA (100 μM).

In contrast to KA receptors, metabotropic glutamate receptors (mGluR) have been reported to be involved in LTD (Calabresi et al. 1992). Because the effect of NS-102 at mGluR is not known to our knowledge, we investigated the involvement of mGluR by coapplication of NMDA with the

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* Afferent activity recorded in 84 neurons were classified according to their response to glutamate (Glu) [expressed as a percent of the N-methyl-D-aspartate (NMDA)-induced current for each neuron]. Neurons were arbitrarily classified as having small Glu-evoked responses of 12 mM Glu-evoked response was <50% of current induced by 100 μM NMDA. A represents activity in myelinated Aδ fibers. C represents activity in unmyelinated C fibers. A + C represents activity in Aδ and C fibers. I represents inhibitory input.

mGluR agonist trans-ACPD (200 μM). However, mGluR activation did not significantly alter the NMDA-induced current (91 ± 3% of control; P > 0.05 Wilcoxon matched pairs test; n = 3).

Description of Glu responses compared with dorsal root input

There was a trend, although not statistically significant (P > 0.05, χ² test), that the majority of neurons with small Glu-induced currents were activated by primary afferent activity in A fibers [A only (33/49) and A + C (9/11)]. Those neurons showing inhibitory input (outward current I; 13/15) also tended to have small Glu-induced currents. On the other hand, there appeared to be no correlation between C only activity and magnitude of Glu-evoked responses. These results are summarized in Table 1.

Effects of Ca²⁺ on Glu-induced currents

Comparison between Glu-induced peak current amplitudes evoked in normal Ca²⁺-containing ACSF and Ca²⁺-free ACSF, respectively, was used to evaluate possible countering effects due to the release of inhibitory neurotransmitters on Glu-evoked responses. Both Ca²⁺-containing ACSF and Ca²⁺-free ACSF contained 1 μM TTX and 10 μM NBQX. Figure 7 illustrates that mean Glu (12 mM)-

![FIG. 6. Potentiating effects of low-affinity KA receptor antagonist, 5-nitro-6,7,8,9-tetrahydrobenzo(G)indole-2,3-dione-3-oxime (NS-102), on Glu-induced currents. A: control traces for Glu (12 mM) and NMDA (100 μM). B: NS-102 (10 μM) potentiated Glu-induced currents. NS-102 was superfused for 20 min in Ca²⁺-free ACSF before B. Calibration bar applies to all panels. Same neuron in A and B. Note that amplitude of NMDA-induced current remains unaltered by NS-102. Agonists were superfused for a duration of 30 s, represented by black bar.](image)

![FIG. 7. Comparison of Glu-induced currents in same neurons evoked in normal Ca²⁺-containing ACSF and in Ca²⁺-free ACSF. Data points represent absolute currents induced by Glu (12 mM; n = 14). Means ± SE are plotted to the left of each data set. Currents evoked in Ca²⁺-free ACSF (△) were statistically significantly larger than corresponding control current in normal ACSF (□, P < 0.01, paired t-test).](image)
induced currents evoked in Ca\(^{2+}\)-free ACSF displayed a small (+38%) but statistically significantly increased peak amplitude compared with corresponding control currents in the same neurons in normal ACSF (440 ± 130 pA and 319 ± 104 pA, respectively; \(P < 0.01\) paired \(t\)-test; \(n = 14\)). However, Glu (12 mM)-induced currents were still significantly smaller compared with NMDA (100 \(\mu M\))-induced currents in Ca\(^{2+}\)-free ACSF (data not shown), which suggests a postsynaptic mechanism.

**DISCUSSION**

These observations indicate the presence of a novel mechanism in rat superficial dorsal horn by which KA receptors induce LTD or SLD of both synaptic- and agent-induced NMDA-receptor–mediated excitatory currents. The findings may relate to classical LTD and add a new mechanism, to the list of potential mechanisms of LTD induction (for reviews, see Asztely and Gustafsson 1996; Linden and Connor 1995) in which Glu, at concentrations sufficient to activate NMDA receptors, can modulate NMDA-induced currents through postsynaptic KA receptors.

Even though Glu-induced currents in the present report were studied at relatively high concentrations, similar to those used by Yajiri et al. (1997), they represent physiologically relevant levels (i.e., micromolar to low millimolar) at the receptor sites considering cellular uptake of Glu in a slice (Garthwaite 1985). In addition, as indicated by the dose-response curves, the Glu concentrations used were sufficient to fully activate NMDA receptors, with NBQX preventing substantial activation of AMPA receptors. This is supported by the observation that most of the 12 mM Glu-induced responses were blocked by MK-801.

Our results show that a substantial proportion of superficial dorsal horn neurons respond to Glu with significantly smaller peak current amplitudes than to NMDA. This differential sensitivity is comparable with previous findings (Näsström et al. 1994), although discrepancies in the number of Glu-responding neurons in these studies may be related to differences in the recording techniques employed (i.e., tight-seal whole cell recording versus sharp intracellular electrodes) and the Glu concentrations used.

Several possibilities exist to account for the observed differences in peak amplitude currents for the two agonists. These are activation of presynaptic inhibitory terminals by Glu and not by NMDA, NMDA receptor desensitization by Glu, and modulation of NMDA receptors by Glu action at non-NMDA receptors.

Glu-induced currents were studied in Ca\(^{2+}\)-containing ACSF as well as Ca\(^{2+}\)-free ACSF to investigate the involvement of presynaptic inhibitory terminals. The observation that Glu-induced currents in Ca\(^{2+}\)-free ACSF were statistically significantly larger than corresponding currents evoked in normal ACSF provides evidence for the possibility that Glu activates the release of inhibitory neurotransmitters by presynaptic neurons. However, this mechanism is insufficient to explain the large differences between Glu and NMDA because the increase was small compared with the differential sensitivity to the agonists. Thus the observation that this differential sensitivity remains, in the presence of TTX and the absence of extracellular calcium, indicates a postsynaptic mechanism.

Despite earlier findings suggesting NMDA receptor desensitization as a possible explanation for lack of Glu effect (Yoshimura and Jessell 1990), we find that coapplication of Glu and NMDA, as well as application of Glu directly before NMDA, results in a depression of NMDA-induced currents that is more closely related to the time course of LTD or STD (lasting minutes to hours) (Pockett 1995; Weisskopf et al. 1993) than receptor desensitization (lasting seconds) (Mayer et al. 1989). A recent report proposed the involvement of low-affinity KA receptors in the depression of NMDA-receptor–mediated currents (Chittajallu et al. 1996). We tested this possibility by applying KA directly before NMDA application. KA mimicked Glu-induced LLD and SLD of NMDA-induced currents.

These findings raise the possibility that Glu-induced NMDA-receptor–mediated currents are depressed via Glu action at KA receptors. This mechanism is a possible explanation for the differential responsiveness to the different NMDA receptor agonists. In contrast to LTD or SLD induced by Glu coapplied with or directly before NMDA, Glu alone induces an acute depression in neurons with small Glu responses. This is supported by the observation that repetitive individual Glu applications at 5-min intervals did not depress subsequent NMDA-induced currents. Thus a particular timing sequence of KA and NMDA receptor activation may be crucial for the induction of LLD and SLD. Such a particular timing sequence is consistent with a anti-Hebbian mechanism of plasticity in which one type of stimulus conditions the system and a second type of stimulus induces a persistent change (for reviews, see Bell et al. 1997; Ekerot and Kano 1989; Linden and Connor 1995). In the present study, it appears as if simultaneous activation of KA and NMDA receptors by Glu only produces an acute depression, whereas a longer-lasting stimulus in sequence at KA and NMDA receptors by KA or Glu plus NMDA results in a long-lasting depression. However, the timing necessary for induction of such long-lasting depression requires further investigation.

The concept of acute depression of Glu-induced NMDA-receptor–mediated currents through activation of KA receptors is strengthened by NS-102 augmentation of Glu-induced currents. NS-102 is suggested to act at GluR6 (Verdoorn et al. 1994) with a high degree of selectivity for low-affinity KA receptors over other ionotropic EAA receptors (Johansen et al. 1993). Therefore, we hypothesize that the complete or partial recovery of Glu currents by NS-102 involves native low-affinity KA receptors composed of GluR6 subunits in either homomeric (Bettler et al. 1992; Egebjerg et al. 1991) or heteromeric (Herb et al. 1992) complexes.

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on elevation of the intracellular Ca\(^{2+}\)-levels (Barry et al. 1996; Cummings et al. 1996). Our observation that Glu-induced currents are depressed in Ca\(^{2+}\)-free medium argues against extracellular Ca\(^{2+}\) influx; however, Ca\(^{2+}\) mobilized from intracellular stores is possible but a less likely mechanism because the intracellular calcium is strongly buffered in the present study.

Interestingly, it has been suggested that KA can induce inactivation of NMDA-receptor–mediated currents through elevation of intracellular calcium (Medina et al. 1994). However, the findings by Medina et al. (1994) are quite different from our findings because their inactivation of NMDA-induced currents by KA was studied in the absence of an AMPA receptor blocker and thus was likely to be partly mediated by activation of AMPA receptors (Bettler and Mulle 1995) and because their inactivation was dependent on the extracellular calcium concentration and disappeared during strong intracellular calcium buffering. It is possible that the comparably slow KA-induced inactivation of NMDA-induced currents reported by Medina et al. (1994) is mediated by two distinct mechanisms, one dependent on elevation of intracellular calcium and a second mechanism, similar to the one in the present study, that is mediated through activation of low-affinity KA receptors.

We found that bath applications of Glu or KA attenuated NMDA-receptor–mediated EPSCs as well as bath-induced currents. This appears consistent with the expression of both low-affinity KA and NMDA receptor subunits on dendrites of superficial dorsal horn neurons (Bonnot et al. 1996) and with findings by Clark et al. (1997) that synaptic and extrasynaptic NMDA receptors behave in a similar manner. It suggests that the present findings have implications for synaptic transmission in this part of the CNS.

Characterization of neurons by their primary afferent input suggests that neurons activated by only A fibers include both types with small or large Glu-induced currents. In contrast, neurons only responding to activity in A fibers may be associated to neurons with small Glu-evoked currents; the latter is in agreement with observations by Schneider and Perl (1985). However, unlike their results, we find that nearly all neurons receiving excitation from both A and C fibers also have small Glu-evoked responses. These results suggest that the majority of neurons activated by A\(_6\) fibers (including A and A + C) may have small Glu-induced currents. One possible explanation for this difference in observation is the difference in recording sites between the two studies; our recordings were in the lateral portion of the SG and those of Schneider and Perl (1985) were more medial. Association of neurons responding with small Glu-evoked currents to A\(_6\) but not C fibers also may relate to the recent findings by Yajiri et al. (1997), who demonstrate a novel presumably EAA-mediated slow synaptic current that is associated with activity in A\(_6\) fibers. This slow synaptic current may relate to the present findings with KA.

Evidence presented here suggests that a fraction of SG neurons that respond to Glu with smaller peak current amplitudes than to NMDA coexpress functional NMDA and low-affinity KA receptors. The KA receptors mediate an excitatory amino acid effect that suppresses NMDA-initiated actions. We propose that this underlies a novel mechanism involving KA receptors in long-lasting depression of NMDA-receptor–mediated currents. Plastic changes are well known to be involved in information storage in the CNS and thus implies a physiological role of KA receptors in long-term modulation of sensory transmission in the superficial dorsal horn.

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