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Ca^{2+}-independent reduction of *N*-methyl-D-aspartate channel activity by protein tyrosine phosphatase

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ABSTRACT **Regulation of ion channel function by intracellular processes is fundamental for controlling synaptic signaling and integration in the nervous system. Currents mediated by *N*-methyl-D-aspartate (NMDA) receptors decline during whole-cell recordings and this may be prevented by ATP. We show here that phosphorylation is necessary to maintain NMDA currents and that the decline is not dependent upon Ca^{2+}. A protein tyrosine phosphatase or a peptide inhibitor of protein tyrosine kinase applied intracellularly caused a decrease in NMDA currents even when ATP was included. On the other hand, pretreating the neurons with a membrane-permeant tyrosine kinase inhibitor occluded the decline in NMDA currents when ATP was omitted. In inside-out patches, applying a protein tyrosine phosphatase to the cytoplasmic face of the patch caused a decrease in probability of opening of NMDA channels. Conversely, open probability was increased by a protein tyrosine phosphatase inhibitor. These results indicate that NMDA channel activity is reduced by a protein tyrosine phosphatase associated with the channel complex.**

Phosphorylation on tyrosine is a common mechanism for regulating protein function; tyrosine phosphorylation has been implicated as a key biochemical event in cellular processes including proliferation, growth, and differentiation (1, 2). Protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs) are expressed at high levels in the developing and mature central nervous system (CNS) (3–5). Tyrosine phosphorylation has been implicated in physiological processes such as synaptogenesis (6) and long-term potentiation (7) and pathophysiological conditions such as ischemia (8). A focus of previous studies has been the actions of PTKs, whereas possible functional roles of PTPs in the CNS remain speculative (5, 9).

In the mammalian CNS, the *N*-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor is a principal receptor in synaptic transmission and in mediating persistent alterations in neuronal function (10). A fundamental understanding that has emerged is that NMDA receptor activity is not fixed but, rather, is dynamically regulated. Regulation through extracellular sites (11–14) and within the ion pore (15, 16) is well-known, but NMDA channels may also be subject to regulation at intracellular sites. Channel activity is modulated intracellularly by Ca^{2+} (17), by interactions with the cytoskeleton (18), and by phosphorylation (19).

Regulation of NMDA receptor function by serine/threonine phosphorylation has been demonstrated: protein kinase C (20–22), and the serine/threonine phosphatases 1/2A (23) and 2B (calcineurin) (24) have been shown to modulate NMDA channel activity. While PTK also has been found to regulate NMDA receptors (25), a functional role for PTP remains to be established. In the present report, we show that PTP is responsible for the decline in NMDA-receptor-mediated currents that has been reported during whole-cell patch clamp recording (19, 26). By using recordings from inside-out patches, we demonstrate that PTP causes a decrease of NMDA single-channel activity, indicating that the target protein is not freely diffusible but rather is integral to or associated with the membrane. Moreover, we provide evidence that the native PTP, and also native PTK, regulating NMDA receptors are associated with the channel complex.

MATERIALS AND METHODS

Cell Culture and Electrophysiology. Primary cultures of spinal dorsal horn were prepared from fetal Wistar rats (embryonic day 17–19) and were used 1–3 weeks after plating as described in detail (27). For recordings, the cultures were bathed in an extracellular recording solution (140 mM NaCl/5.4 mM KCl/25 mM Hepes/1.3 mM $CaCl_2$/33 mM glucose/0.001 mM glycine/0.001 mM tetrodotoxin, pH 7.35 and osmolarity 310–320 mosM). To remove the blockade of NMDA channels by Mg^{2+} (15, 16), Mg^{2+} was not added to the extracellular solution except where indicated. For whole-cell recording, pipettes (2–5 MΩ) were filled with a standard intracellular solution [140 mM CsCl/10 mM Hepes/10 mM bis(2-aminophenoxy)ethane-*N,N,N′,N′*-tetraacetic acid (BAPTA), pH 7.25 and osmolarity 300–315 mosM]. The intracellular solution was supplemented as required with 2 mM $MgCl_2$, 4 mM K_2-ATP, peptide A, truncated T-cell PTP, or recombinant $pp60^{c\text{-}src}$. With the perforated patch configuration, pipettes were double-filled by using intracellular solution supplemented with nystatin (100 μg/ml). NMDA-receptor-mediated whole-cell currents were evoked at regular intervals by pressure application (150 kPa, 100 ms) of L-aspartate (250–500 μM) from a micropipette with its tip located 20–30 μm from the cell under study. The holding potential was −60 mV unless otherwise indicated.

For single-channel recordings, the inside-out patch configuration was used. The recording pipettes (10–20 MΩ) were filled with a solution [110 mM Na_2SO_4/10 mM Cs_2SO_4/25 mM Hepes/1.3 mM $CaCl_2$/33 mM glucose/0.01 mM NMDA/0.003 mM glycine, pH 7.35 and osmolarity 310–320 mosM]. The solution bathing the intracellular side of the patch was 140 mM CsCl/10 mM Hepes/1 mM $CaCl_2$/10 mM BAPTA/2 mM $MgCl_2$/4 mM K_2ATP, pH 7.25 and osmolarity 310–320 mosM. This solution was supplemented as required with T-cell PTP (40–80 nM) or sodium orthovanadate (100 μM). The holding potential of the patch was +70 mV unless otherwise indicated. Current records were filtered at 10 kHz (−3 dB), digitized at a rate of 94 kHz, and stored on tape. We observed single channels with conductance levels in the range of 40–60 pS and

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Abbreviations: ATP[γS], adenosine 5′-[γ-thio]triphosphate; p[NH]ppA, adenosine 5′-[β,γ-imido]triphosphate; BAPTA, bis(2-aminophenoxy)ethane-*N,N,N′,N′*-tetraacetic acid; NMDA, *N*-methyl-D-aspartate; PTK, protein tyrosine kinase; PTP, protein tyrosine phosphatase; CNS, central nervous system.

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15–30 pS, as is typically observed with NMDA channels in other mammalian central neurons (28). The reversal potential was near 0 mV and the channels showed a voltage-dependent block by applying the NMDA receptor antagonist ketamine in the bathing solution (23). Therefore, we conclude that recordings were from NMDA receptor single channels.

Data Analysis. Whole-cell currents were analyzed from raw data stored on computer. For single-channel data, recordings were replayed from tape, filtered at 2–5 kHz (−3 dB, 8-pole Bessel), and sampled continuously at 20 kHz onto an IBM-PC-compatible computer. Channel openings and closings were determined off-line by using a 50% crossing threshold. Openings or closings ≤100 μs were not included in the analysis. The amplitude of the single-channel currents was calculated from an all-points histogram as the difference between the mean of the baseline and that of the open-channel current. The probability of channel opening (P_o) was calculated as the ratio of the total channel-open time to total time. Channel activity during a control period of 5–10 min immediately preceding enzyme or inhibitor application was compared with activity during a similar period beginning 2–5 min after the start of the application. Data are presented as percentage of control.

Sources of Chemicals. Peptide A was purchased from Bachem; purified recombinant human $pp60^{c\text{-}src}$ was from Upstate Biotechnology Inc. (Lake Placid, NY); genistein and calyculin A were from LC Laboratories (Woburn, MA); and BAPTA was from Molecular Probes. Truncated T-cell PTP was a gift from E. Fisher, University of Washington, Seattle, WA. All other chemicals were from Sigma.

RESULTS

NMDA Currents Are Maintained by ATP and Adenosine 5′-[γ-thio]Triphosphate (ATP[γS]) but not by Adenosine 5′-[β,γ-imido]Triphosphate (p[NH]ppA). During whole-cell recordings made using the standard intracellular solution, NMDA currents gradually declined and reached a stable level within the first 20 min of recording. This progressive decline, which has been referred to as rundown (19, 29, 30), is illustrated in Fig. 1*A*. The responses were maintained at the stable level for as long as the recording persisted, up to 4 h in some cases. On average, the peak amplitude of the currents stabilized at 49 ± 2% (mean ± SEM; n = 11) of that of the initial response and the time constant of the decline was 355 s. In contrast to whole-cell recordings, NMDA currents did not decline during recordings made by using the perforated-patch technique (n = 12). Moreover, NMDA currents did not run down during whole-cell recording when MgATP (4 mM) was included in the standard intracellular recording solution. Rather, the currents transiently increased during the first 5 min of recording and gradually stabilized at 105 ± 5% of the initial amplitude (n = 13 cells). Thus, in dorsal horn neurons depletion of intracellular ATP may be sufficient to account for the rundown of NMDA currents.

We examined the possibility that ATP prevents the rundown of NMDA currents by supporting protein phosphorylation. Two ATP analogues were used: ATP[γS], which donates thiophosphate in phosphorylation reactions thereby substituting for ATP (31), and p[NH]ppA, which has a nonhydrolyzable γ-phosphate and, therefore, cannot substitute for ATP in phosphorylation reactions. As illustrated in Fig. 1*A*, NMDA currents were maintained when MgATP[γS] (4 mM) was added to the standard intracellular recording solution; after 20 min of recording the currents were 116 ± 9% (n = 6) of the initial amplitude. In contrast, NMDA currents declined to 61 ± 13% when Mgp[NH]ppA (4 mM; n = 5) was used. Thus, protein phosphorylation may be required to maintain NMDA currents and the rundown may be due to dephosphorylation.

Rundown of NMDA Currents Is Not Dependent on Ca^{2+}. Loss of ATP might have caused the decline in NMDA currents

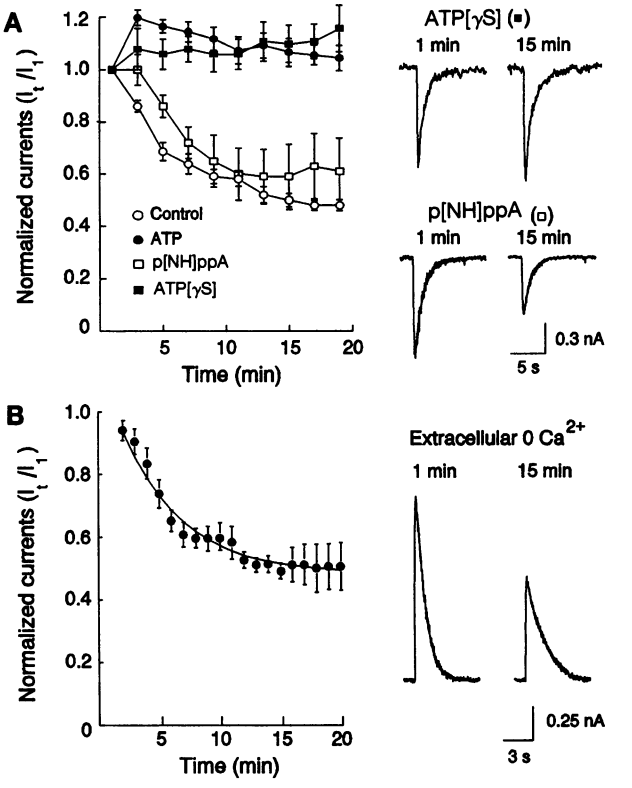

FIG. 1. ATP[γS], but not p[NH]ppA, prevents rundown of NMDA currents and rundown persists when extracellular Ca^{2+} is removed. (*A*) Plotted in the graph is I_t/I_1, the ratio of the peak amplitude of the NMDA current at time t over that of the initial current I_1. Recordings made with the standard intracellular solution (○; n = 11) or with standard solution supplemented with MgATP (4 mM, ●; n = 13), with 4 mM ATP[γS] (■; n = 6), or with 4 mM p[NH]ppA (□; n = 5). Representative traces taken at the times indicated from neurons studied with intracellular solution containing ATP[γS] or p[NH]ppA are shown on the right. (*B*) Normalized peak currents are plotted in the graph for recordings made with 0 Ca^{2+}/100 μM BAPTA extracellular solution (●; n = 5 cells). The smooth curve is the best single exponential fit to the mean data; τ = 283 s. The traces on the right show currents recorded at the time points indicated above each trace from a neuron studied when the extracellular solution contained no added Ca^{2+} and 100 μM BAPTA. Note that the membrane potential was held at +40 mV and, therefore, NMDA currents were outward.

by allowing intracellular levels of Ca^{2+} to rise thereby triggering Ca^{2+}-dependent processes. However, we have found that the currents decrease even when the Ca^{2+} buffering capacity of the intracellular solution is increased sufficiently to maintain low levels of intracellular Ca^{2+} concentration (26). Because of influx of Ca^{2+} through NMDA channels, it is possible that in microdomains near the inner mouth of the channel there may have been localized increases in Ca^{2+} concentration that might have been undetected in previous experiments where the intracellular Ca^{2+} concentration was averaged over the entire cell soma. Such localized increase in the intracellular Ca^{2+} concentration could be sufficient to activate Ca^{2+}-dependent processes that might down-regulate the function of NMDA channels. To investigate this possibility, we did experiments using extracellular solution with no added Ca^{2+} and containing 100 μM BAPTA. Exposing dorsal horn neurons to a 0 Ca^{2+}/100 μM BAPTA solution evoked a sustained inward current of 2–3 nA and produced a severe deterioration of the recording within several minutes. We found that adding Mg^{2+} (1 mM) to the extracellular solution prevented this current and preserved long recordings. Because it was necessary to include Mg^{2+}, we held the membrane potential at +40 mV, which removed the Mg^{2+} blockade of NMDA currents and thereby

allowed the currents to be monitored throughout the recording period. As shown in Fig. 1*B*, under these conditions NMDA currents declined to a stable level 50 ± 9% (mean ± SEM) of the initial level (n = 5 cells). The time constant for the decline in the peak current was 283 s. Thus, the 0 Ca^{2+}/100 μM BAPTA extracellular solution did not prevent or slow the rundown of NMDA currents.

A PTP Overcomes the Effect of ATP. We considered that the rundown might be due to either serine/threonine or tyrosine dephosphorylation. We found that NMDA currents recorded by using the perforated-patch method were unaffected by calyculin A, an inhibitor of serine/threonine phosphatases 1 and 2A (32), at concentrations up to 100 nM (n = 6 cells). Thus, these serine/threonine phosphatases were unlikely to have accounted for the rundown of NMDA currents. The Ca^{2+} independence of the rundown indicates further that it is not due to calcineurin, a Ca^{2+}-dependent serine/threonine phosphatase. We therefore investigated directly whether PTP activity may depress NMDA currents. We intracellularly administered a truncated form of T-cell PTP in which the regulatory domain has been removed and which, therefore, acts on phosphotyrosine residues in a broad range of proteins (33). As shown in Fig. 2, T-cell PTP (40 nM) produced a gradual decline in NMDA currents during recordings with intracellular solution containing ATP; the steady-state level was 67 ± 6% of the initial amplitude (n = 5 cells). After the currents had reached a steady level, the current–voltage relationship was found to be nearly linear and the reversal potential was −5 to 0 mV (n = 3 cells). The reversal potential was similar in neurons recorded without T-cell PTP (n = 6) or with the perforated-patch technique (n = 5), suggesting that T-cell PTP had caused a reduction in the NMDA-receptor-activated conductance rather than a change in the driving force. When T-cell PTP was boiled for 10 min prior to its addition to the intracellular recording solution, the amplitude of NMDA currents was maintained, indicating that active PTP is required to induce the decline.

A Peptide Inhibitor of PTK Causes a Decline of NMDA Currents. The hypothesis arising from the preceding observations is that the rundown of NMDA currents is caused by tyrosine dephosphorylation resulting from unopposed PTP activity when ATP is lost from the cell. An alternative route to revealing activity of PTPs is to inhibit PTKs. We intracellularly applied peptide A, an inhibitor of PTKs but not of protein serine/threonine kinases (34), during recordings in which ATP was also included. Peptide A (100 μM) induced a progressive decline in the amplitude of NMDA currents (Fig. 3). Within 15 min of the onset of recording, the currents decreased to 63 ± 6% of the initial amplitude (n = 8 cells) and remained stable at this level. To investigate the biological activity of peptide A, we tested it against the PTK $pp60^{c\text{-}src}$, which potentiates NMDA currents (25). We found that the potentiation caused by $pp60^{c\text{-}src}$ (30 units/ml) was blocked by coadministering

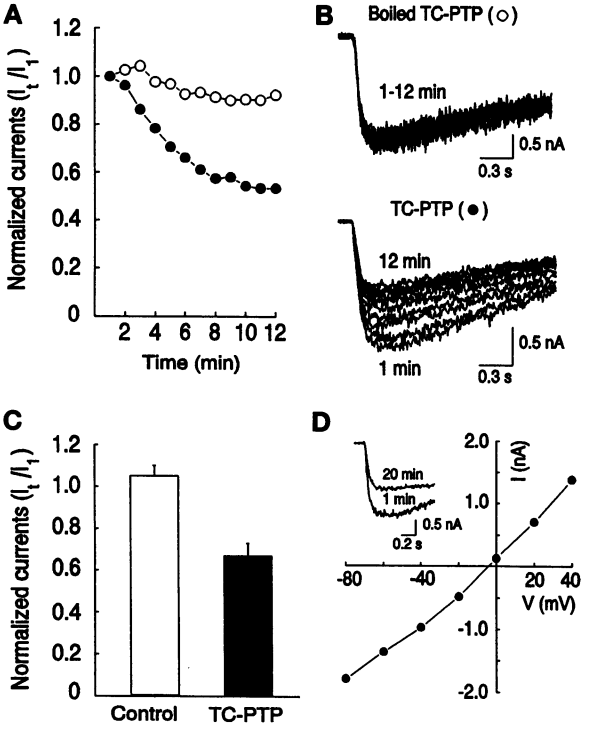

FIG. 2. T-cell PTP causes a decrease in whole-cell NMDA currents. (*A*) Normalized peak NMDA currents are plotted for neurons recorded in presence of active (●) or heat-inactivated (○) T-cell PTP (TC-PTP; 40 nM) in the intracellular recording solution, which also contained 4 mM MgATP. (*B*) Superimposed individual current traces from neurons shown in *A*. (*C*) Histogram showing mean I_{20}/I_1 from neurons recorded with ATP-containing intracellular solution (control) and with the intracellular solution supplemented with TC-PTP (n = 5). *D* is the current–voltage (*I–V*) curve of NMDA currents constructed from a neuron studied with TC-PTP in the intracellular solution. NMDA currents were evoked at a series of membrane potentials from −100 to +60 mV in increments of 20 mV after the responses had stabilized. NMDA currents were 62% of the initial amplitude as shown (*Inset*) by the superimposed individual responses taken at 1 min and 20 min.

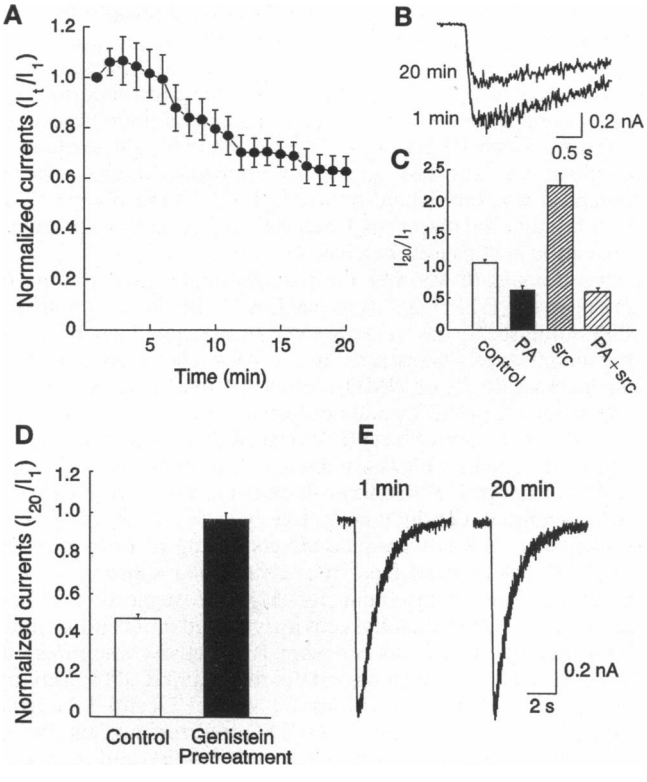

FIG. 3. Inhibiting PTK activity overcomes the effect of ATP causing NMDA currents to rundown, and pretreating neurons with genistein prevents the rundown of NMDA currents when ATP is not included in the intracellular solution. (*A*) I_t/I_1 is plotted for neurons recorded in the presence of 100 μM peptide A and 4 mM ATP (n = 7). (*B*) Superimposed individual traces taken at the times indicated from a neuron recorded with a pipette solution containing peptide A (100 μM) and ATP (4 mM). (*C*) Histogram showing average I_{20}/I_1 from neurons recorded with ATP-containing intracellular solution (control) or this intracellular solution supplemented with peptide A (PA), $pp60^{c\text{-}src}$ (src, 30 units/ml; n = 8), or $pp60^{c\text{-}src}$ plus peptide A (PA + src; n = 6). (*D*) In the histogram, the mean I_{20}/I_1 are shown for neurons prior to (control, n = 11) or during treatment with genistein (100 μM). (*E*) Representative traces taken at the times indicated from a neuron treated with genistein.

peptide A (Fig. 3*C*), indicating its activity as a PTK inhibitor under our experimental conditions.

Pretreatment with a Membrane-Permeant PTK Inhibitor Occludes Rundown. If the rundown of NMDA currents is due to progressive loss of the cell's ability to maintain tyrosine phosphorylation, then it is predicted that inhibiting PTKs prior to recording would preempt any further decrease caused by loss of ATP. We tested this by treating neurons with genistein (100 μM), a membrane-permeant PTK inhibitor, for 10–15 min, before starting whole-cell recording. The standard intracellular recording solution, without ATP, was used and 100 μM genistein was added to ensure that its intracellular concentration was consistent. In contrast to all other recordings made with intracellular solutions lacking ATP, NMDA currents were stable when cells were pretreated with genistein (Fig. 3 *D* and *E*): the amplitude of the currents was 97 ± 3% (n = 5) of the initial level after 20 min of recording. In cells not treated with genistein, NMDA currents declined to a steady-state level ≈50% of the initial amplitude.

NMDA Single-Channel Activity Is Depressed by Truncated T-Cell PTP and Is Increased by a PTP Inhibitor. To investigate whether the target protein for PTP was diffusible or membrane-associated, we made single-channel recordings by using the inside-out patch configuration and applied agents to the cytoplasmic face of the membrane. NMDA channel activity was elicited by continuous exposure of the extracellular face of the membrane to NMDA itself in the presence of glycine. We found that applying T-cell PTP to the cytoplasmic face of the patch produced a decrease in P_o in all patches tested (n = 4), as illustrated in Fig. 4*A*. On average T-cell PTP caused P_o to decrease to 50 ± 17% of that during the control period just prior to applying the phosphatase. The mean open time after applying T-cell PTP was 91 ± 3% of control. Single-channel conductance was 103 ± 4% of control and the reversal potential was unaffected by T-cell PTP. These observations indicate that the target for T-cell PTP is a protein, or proteins, present in the excised patches.

To investigate whether the patches might also contain an endogenous PTP regulating NMDA channels, we applied a PTP inhibitor, orthovanadate (35), to the cytoplasmic face of the membrane. As illustrated in Fig. 4*B*, orthovanadate caused an increase in P_o of NMDA single-channel currents. P_o increased in all of the six patches tested; on average, P_o was 197 ± 18% of the control level ($P < 0.05$, Wilcoxon sign rank test). The mean open time was also increased by orthovanadate (125 ± 6% of control; $P < 0.05$), whereas there was no change in single-channel conductance (105 ± 5% of control). Orthovanadate did not produce effects during recordings when MgATP was omitted from the intracellular solution (n = 4 patches). The requirement for MgATP suggests that the increase in NMDA channel activity is caused by an endogenous PTK that may act unopposed when PTP activity is suppressed.

To ensure that orthovanadate may inhibit PTP activity under our recording conditions, we applied T-cell PTP during exposure to orthovanadate (100 μM) in three patches. When T-cell PTP was applied with orthovanadate, P_o and the mean open time were found to be 83 and 107%, respectively, compared with orthovanadate application alone. Thus, the effect of T-cell PTP on NMDA channels was attenuated by orthovanadate.

DISCUSSION

The nearly 50% decline in NMDA currents observed during whole-cell recordings demonstrates that intracellular regulatory processes may provide substantial ongoing modulation of NMDA receptor function. This decline in NMDA currents could not be attributed to Ca^{2+} because the currents decreased even when intracellular buffering of Ca^{2+} was increased (26) and when extracellular Ca^{2+} was removed. The currents were

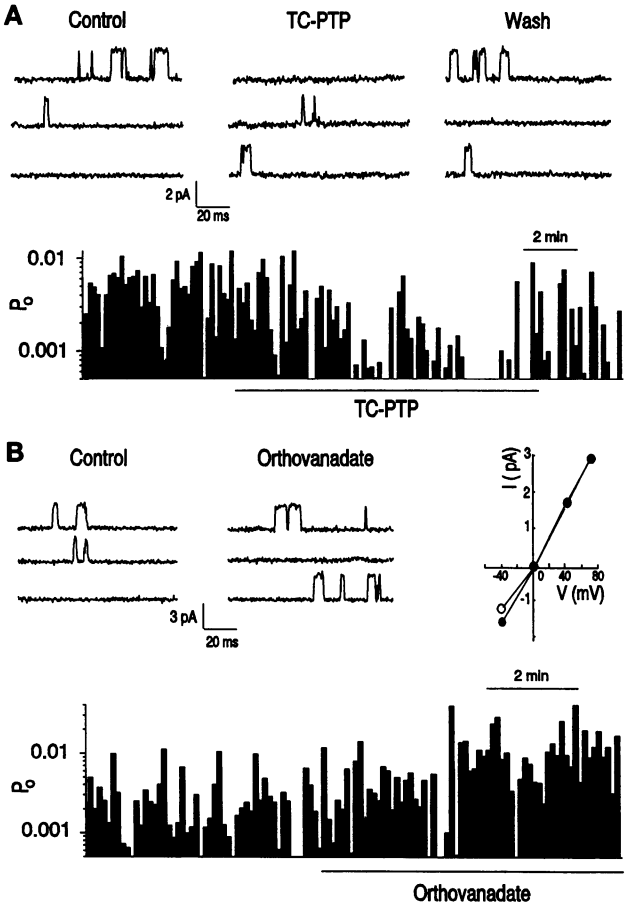

FIG. 4. NMDA single-channel activity in inside-out patches is reduced by T-cell PTP (*A*) and increased by orthovanadate (*B*). T-cell PTP (80 nM) or sodium orthovanadate (100 μM) was applied to the cytoplasmic side of the patch. (*A*) Current traces were taken before (Control), during (TC-PTP), and after (Wash) the application of T-cell PTP. The continuous time histogram shows open probability (P_o) calculated in bins of duration 10 s. T-cell PTP was applied during the period indicated by the bar below the histogram. Values for mean open time and P_o: control, 1.31 ± 0.04 ms and 5.07 × 10^{-3}; T-cell PTP, 1.33 ± 0.04 ms and 1.33 × 10^{-3}, respectively. (*B*) (*Upper Left*) Current traces are shown before (Control) and during application of orthovanadate. (*Right*) Mean single-channel current amplitude (I) vs. holding potential (V). Data points were calculated from 1 min of recording at each potential before (○) or during (●) application of orthovanadate. Below is a continuous time histogram of P_o; orthovanadate was applied as indicated by the bar. Mean open time and P_o: control, 2.39 ± 0.05 ms and 4.42 × 10^{-3}; orthovanadate, 2.49 ± 0.06 ms and 11.0 × 10^{-3}, respectively.

maintained by ATP[γS], as well as by ATP, but not by p[NH]ppA, suggesting that the principal requirement for supporting the currents is phosphorylation. The depression of the currents by intracellular administration of T-cell PTP indicates that PTP activity is sufficient to cause a reduction in NMDA receptor function. Moreover, since peptide A also produced a decline in NMDA currents, loss of PTK activity is also sufficient. Finally, protein tyrosine phosphorylation appears to be required because pretreating the cells with a PTK inhibitor occluded the decline in currents that occurred in the absence of ATP. Thus, the present results indicate that protein tyrosine dephosphorylation is necessary and sufficient to account for the decline of NMDA currents.

The NMDA receptor complex itself may be the target for PTKs or PTPs, and the primary sequence of cloned NMDA receptor subunits (36) indicates that each contains potential sites for tyrosine phosphorylation (37). However, membrane patches are known to contain various proteins, including ion

channels, regulatory proteins, enzymes, and even cytoskeletal elements (38), and thus other possible targets cannot be eliminated. Nonetheless, biochemical study of postsynaptic density proteins from adult brain has indicated that NMDA-R2B (39) is phosphorylated on tyrosine. Whether the tyrosine phosphorylation of NMDA receptor subunits is the mechanism by which channel activity is regulated, however, remains to be determined.

Our observations with the PTP inhibitor orthovanadate indicate that NMDA channel activity is tonically regulated by an endogenous PTP that is present in the patches. Receptor PTPs are membrane-spanning proteins (2) and, therefore, it is clear that they could be readily incorporated into patches. Nonreceptor PTPs also might be present in the patches either by being directly linked to the membrane or by protein–protein interactions (40). The PTP gene family appears to be large with a diversity and complexity matching that of the tyrosine kinases, which are estimated to number in the thousands (41). The endogenous PTP that regulates NMDA channel activity might be one of the PTPs that have been identified in the CNS or, since only a relatively small number of PTPs have been identified, a novel PTP.

While the present results clearly indicate that the decrease in NMDA channel function produced by PTP is Ca^{2+}-independent, NMDA channels may also be regulated by a dephosphorylation that is Ca^{2+}-dependent. For example, NMDA channel activity has been found to be decreased by calcineurin, a serine/threonine phosphatase (24), which requires activation by Ca^{2+}/calmodulin. In contrast, Ca^{2+}-dependent processes that are separate from phosphorylation have been reported to regulate NMDA receptors. In cultured rat hippocampal neurons, a rundown of NMDA currents is blocked by high intracellular levels of BAPTA or by removing extracellular Ca^{2+}, whereas this rundown is not prevented by ATP[γS] (30). Phalloidin also was found to prevent this depression of NMDA currents, suggesting that it is caused by actin depolymerization (18). The Ca^{2+}-independent rundown reported presently is not prevented by phalloidin (Y.T.W. and M.W.S., unpublished results). Thus, there are distinct Ca^{2+}-dependent, as well as Ca^{2+}-independent, intracellular mechanisms that may regulate NMDA channel function.

Tyrosine phosphorylation/dephosphorylation is common in signaling pathways for a diversity of molecules including growth factors (42), cytokines (43), and neurotransmitters (44, 45). Activating such pathways may result in lasting changes in the CNS. It is possible that tyrosine phosphorylation/dephosphorylation is a point where various signaling pathways come together and produce sustained alterations in the activity of NMDA channels.

In summary, the present results demonstrate that NMDA channel activity is regulated by a PTP associated with the channel complex. We suggest that through regulating the activity of the postsynaptic NMDA receptors, PTPs may modulate the efficacy of synaptic transmission. Because NMDA receptors, as well as PTPs and PTKs, are expressed widely in the CNS, the modulation of NMDA channels by tyrosine phosphorylation/dephosphorylation may be a link in synaptic plasticity in a diversity of neuronal systems.

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