Most voltage-gated Na\textsuperscript{+} channels inactivate almost completely at depolarized membrane potentials, but in some cells a residual Na\textsuperscript{+} current is seen that is resistant to inactivation. This persistent Na\textsuperscript{+} current can have a profound impact on the electrical behavior of excitable cells, and the regulation of this property could have important biological consequences. However, the biological signaling mechanisms that regulate the persistence of Na\textsuperscript{+} channels are not well understood. This study showed that in nerve terminals and ventricular myocytes nitric oxide (NO) reduced the inactivation of Na\textsuperscript{+} current. This effect was independent of cGMP, was blocked by N\textsuperscript{-}ethylmaleimide, and could be elicited in cell-free outside-out patches. Thus, a reactive nitrogen species acts directly on the channel or closely associated protein. Persistent Na\textsuperscript{+} current could also be induced by endogenous NO generated enzymatically by NO synthase (NOS). Application of ionomycin to raise the intracellular Ca\textsuperscript{2+} concentration in myocytes activated NOS. The NO produced in response to ionomycin was detected with an NO-sensitive fluorescent dye. Persistent Na\textsuperscript{+} current was enhanced by the same treatment, and NOS inhibitors abolished both the elevation of NO and the induction of persistent Na\textsuperscript{+} current. These experiments show that NO is a potential endogenous regulator of persistent Na\textsuperscript{+} current under physiological and pathophysiological conditions.

According to the classical Hodgkin-Huxley model, Na\textsuperscript{+} channels inactivate within a few milliseconds after being activated by a depolarizing voltage step. This together with the opening of K\textsuperscript{+} channels leads to rapid membrane repolarization to terminate an action potential. However, many excitable tissues have a component of Na\textsuperscript{+} current that is resistant to inactivation. This “persistent” Na\textsuperscript{+} current is believed to play important roles in the integration of synaptic inputs (1, 2), the generation of rhythmic oscillations (1, 3, 4), and the pathological changes in electrical excitability associated with many disease states including cardiac arrhythmias, ischemic stroke, and epilepsy (5–7). NO donors have recently been shown to increase persistent Na\textsuperscript{+} current in posterior pituitary nerve terminals (8) and hippocampal neurona (9). NO levels rise following Ca\textsuperscript{2+} overload and ischemia, and Na\textsuperscript{+} current persistence is enhanced by hypoxia (10). Because these conditions promote arrhythmias and seizures, it is possible that NO-induced Na\textsuperscript{+} channel persistence is involved.

The action of NO on Na\textsuperscript{+} channels is through a direct chemical reaction with a protein thiol (8, 9). NO has been shown to modulate a number of other ion channels by this mechanism (11–14). However, little evidence has been presented that endogenous NO can initiate this process. Indeed, since the proposal that NO can modify protein thiols (15), an important question has been the extent to which this represents a biological route for the modulation of function. In the case of Ca\textsuperscript{2+}-activated K\textsuperscript{+} channels in vascular smooth muscle, acetylcholine was shown to mimic the effect of NO (11). Here we show that NO induces persistent Na\textsuperscript{+} currents in ventricular myocytes and neurohypophysial nerve terminals. We further show that endogenous NO production can be stimulated in myocytes by Ca\textsuperscript{2+} loading. This induces persistent Na\textsuperscript{+} current similar to that produced by exogenous NO application. Both rises in cellular NO and modulation of Na\textsuperscript{+} channels were blocked by inhibitors of nitric-oxide synthase (NOS). Thus, endogenously generated NO can induce persistent Na\textsuperscript{+} current. These findings suggest that NO is a potential physiological regulator of Na\textsuperscript{+} channel persistence, and this is likely to have important consequences for the regulation of cellular excitability.

**MATERIALS AND METHODS**

**Posterior pituitary slices** were prepared from male Harlan Sprague-Dawley rats (200–300 g) as described previously (16). Slices were maintained in 95% O\textsubscript{2}/5% CO\textsubscript{2}-saturated artificial cerebrospinal fluid containing 125 mM NaCl, 26 mM NaHCO\textsubscript{3}, 1.25 mM NaH\textsubscript{2}PO\textsubscript{4}, 2 mM CaCl\textsubscript{2}, 1 mM MgCl\textsubscript{2}, and 10 mM glucose. Adult rat ventricular myocytes were isolated enzymatically by perfusion of the heart with 125 mM NaCl, 4 mM KCl, 26 mM NaHCO\textsubscript{3}, 1.25 mM NaH\textsubscript{2}PO\textsubscript{4}, 2 mM CaCl\textsubscript{2}, 1 mM MgCl\textsubscript{2}, and 10 mM glucose. The heart was then perfused with 125 mM NaCl, 4 mM KCl, 26 mM NaHCO\textsubscript{3}, 1.25 mM NaH\textsubscript{2}PO\textsubscript{4}, 2 mM CaCl\textsubscript{2}, 2 mM EGTA, 10 mM NaH\textsubscript{2}PO\textsubscript{4}, and 10 mM glucose. Ventricular myocytes were isolated from the aorta using a 125 mM NaCl, 4 mM KCl, 26 mM NaHCO\textsubscript{3}, 1.25 mM NaH\textsubscript{2}PO\textsubscript{4}, 2 mM CaCl\textsubscript{2}, and 10 mM glucose perfusion. Slices and myocytes were perfused with artificial cerebrospinal fluid containing 125 mM NaCl, 4 mM KCl, 26 mM NaHCO\textsubscript{3}, 1.25 mM NaH\textsubscript{2}PO\textsubscript{4}, 2 mM CaCl\textsubscript{2}, 1 mM MgCl\textsubscript{2}, and 10 mM glucose. Adult rat ventricular myocytes were isolated from the aorta by perfusion of the heart with 125 mM NaCl, 4 mM KCl, 26 mM NaHCO\textsubscript{3}, 1.25 mM NaH\textsubscript{2}PO\textsubscript{4}, 2 mM CaCl\textsubscript{2}, and 10 mM glucose. Adult rat ventricular myocytes were isolated from the aorta by perfusion of the heart with 125 mM NaCl, 4 mM KCl, 26 mM NaHCO\textsubscript{3}, 1.25 mM NaH\textsubscript{2}PO\textsubscript{4}, 2 mM CaCl\textsubscript{2}, and 10 mM glucose. Adult rat ventricular myocytes were isolated from the aorta by perfusion of the heart with 125 mM NaCl, 4 mM KCl, 26 mM NaHCO\textsubscript{3}, 1.25 mM NaH\textsubscript{2}PO\textsubscript{4}, 2 mM CaCl\textsubscript{2}, and 10 mM glucose.

**Voltage clamp recordings** were recorded using standard patch clamp methods (18). Patch pipettes with resistances between 2 and 3 M\textOmega were prepared from borosilicate or aluminosilicate glass (Garner Glass, Claremont, CA). Series resistance compensation was routinely set at 50–70%. Leak conductance was subtracted using a P/4 protocol. In nerve terminals, voltage errors due to R\textsubscript{e} errors were generally <500 pA, so that R\textsubscript{e} errors were generally ~1 mV or less when persistent Na\textsuperscript{+} current was measured.

In nerve terminals, the bathing solution contained 121 mM NaCl, 20 mM tetrathylylammonium, 10 mM HEPES, 10 mM glucose, 4 mM CsCl, 2 mM 4-aminopyridine, 2 mM CaCl\textsubscript{2}, 1 mM MgCl\textsubscript{2}, and 0.2 mM CaCl\textsubscript{2}. The pipette solution contained 120 mM KCl or CsCl, 10 mM NaCl, 10 mM tetrathylammonium, 10 mM HEPES, 5 mM EGTA, 1 mM MgATP, and 0.1 mM GTP, pH 7.3. For excised, outside-out patch recording from nerve terminals, the bath contained artificial cerebrospinal fluid solution, and the pipette solution was as above with 120 mM CsCl. For myocyte patch clamp recording, the bathing solution contained 130 mM NaCl, 10 mM HEPES, 5 mM KCl, 5 mM CsCl, 5 mM CaCl\textsubscript{2}, 2 mM CaCl\textsubscript{2}, 2 mM MgCl\textsubscript{2}, 0.1 mM CaCl\textsubscript{2}, 0.1 mM EGTA, and 5 mM HEPES.

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Nitric Oxide Induction of Persistent Sodium Channels

RESULTS

Na+ currents were recorded in the nerve terminals of the posterior pituitary and in ventricular myocytes. Under control conditions, depolarizing pulses evoked a transient current, and after the transient phase ended there was little current detectable above base line. After NO treatment, inactivation was incomplete; the transient Na+ current was followed by a persistent Na+ current (Fig. 1, A and B). A further increase in persistent current (up to ~10% of peak current) could then be elicited by additional NO treatment (Fig. 1B), and no recovery was evident for the duration of the recording (~20 min). The persistent current inactivated only slightly during the course of a 200-ms pulse (Fig. 1B) but deactivated rapidly upon repolarization to ~80 mV. NO had similar effects in all nerve terminals (n = 15) and myocytes (n = 29) tested, with a mean persistent current density of 26.1 ± 2.6 pA/pF and 5.3 ± 0.3 pA/pF, respectively, elicited by photolysis of SNP (Fig. 2B). The UV light used to release NO had no effect on its own. Further, no effects of photolysis were observed when the caged NO solution was exposed to light prior to recording, presumably because prior illumination photolyzed the caged NO. Because NO itself has a short lifetime in the presence of oxygen it decomposed prior to patch recording. Whole terminal recording solution was exposed to light prior to recording, presumably because prior illumination photolyzed the caged NO. Because NO itself has a short lifetime in the presence of oxygen it decomposed prior to patch recording. Whole terminal recording solution contained 130 mM cesium gluconate, 10 mM NaCl, 10 mM HEPES, 13 mM tetraethylammonium, 10 mM EGTA, and 4 mM MgATP, pH 7.4.

Either 1 or 4 mM dipotassium nitrosylpentachlororuthenate (K2RuCl5NO; Molecular Probes, Eugene, OR) or 2 mM sodium nitroprusside (SNP; Sigma) were used as caged NO. Each was included in the pipette solution. After establishment of a whole terminal recording, at least 2–3 min were allowed for diffusion of caged NO into the nerve terminal prior to photolysis. The preparation was illuminated with a 75 W Xe arc lamp (Optiphip, Highland Mills, NY) gated by an electromechanical shutter. We have previously calibrated the photolytic efficiency of this system by measuring the light-induced increase in the fluorescence of caged fluorescein (fluorescein bis-(5-carboxymethoxy-2-nitrobenzyl) ether) (14). We have previously calibrated the photolytic efficiency of this system by measuring the light-induced increase in the fluorescence of caged fluorescein (fluorescein bis-(5-carboxymethoxy-2-nitrobenzyl) ether) (14). From these experiments we have estimated that one light flash will convert ~2% of the K2RuCl5NO to free NO. With 4 mM K2RuCl5NO, we estimate that five flashes of light in rapid succession (our typical illumination protocol) would produce [NO] ~400 μM.

For fluorometric monitoring of NO rises, cells were preloaded with diaminofluorescein (19) (DAF-2; Calbiochem, San Diego, CA) by incubating in 5 μM DAF-2-DA (the diacetate ester) for 20 min. Fluorescence was measured from single cells with a Deltascan spectrofluorometer (Photon Technology, Int., South Brunswick, NJ) coupled to a Reichert Jung Diastar microscope (Leica, Deerfield, IL). The excitation light was tuned to 488 nm and reflected onto the preparation by a 518-nm dichroic mirror. Emitted light was passed through a 550 ± 25-nm bandpass filter, measured with a photomultiplier tube and read into a computer. Parallel runs were performed on DAF-2-loaded cells on a Bio-Rad 1024 confocal microscope. All other drugs and reagents were obtained from Sigma/RBI. All values are expressed as the means ± S.E. Statistical significance was evaluated using a two-tailed Student’s t test.
Nitric Oxide Induction of Persistent Sodium Channels

A. NO application at concentrations of 1–2 mM, and SNP, activated sodium channels with an apparent 

B. NO application at concentrations of 1–2 mM, and SNP, activated sodium channels with an apparent 

FIG. 2. Persistent Na$^+$ current was activated by different forms of NO application and blocked by NEM. A, the sulfhydryl alkylating reagent NEM (5 mM, 3 min) reduced the effect of NO in myocytes (photolysis of SNP). Current was activated by 200-ms voltage pulses from −95 to −35 mV. B, summary of NO activation of persistent Na$^+$ current in nerve terminals and myocytes. Currents were evoked by pulses from −120 to −20 mV (100 ms) in terminals and as stated above in myocytes. NO was applied by photolysis of K$_3$RuCl$_6$NO (p < 0.001) and SNP (p < 0.001) and by addition of diethylamine NONOate (DEA-NO, 1–2 mM, p < 0.001). Pretreatment with NEM (5 mM) prevented the persistent Na$^+$ current caused by NO (photolysis of SNP) in a time-dependent manner (<5 min, p < 0.001; >10 min, p < 0.001; number of experiments in parentheses above each bar).

Potential of 65 mV, which is very close to the Na$^+$ Nernst potential calculated for the solutions used in these experiments ($E_{Na^+} = 69$ mV). Fig. 1E shows that steady-state inactivation was incomplete in NO-modified channels, with ~6% of the maximal current remaining at positive potentials. Plots of the voltage dependence of Na$^+$ conductance (Na$^+$ current divided by $V - E_{Na^+}$; Fig. 1D) show that the NO-modified transient current and the persistent current were shifted to the left (negative) by 3 and 11 mV, respectively, relative to the control transient current. These negative shifts are an important hallmark of persistent Na$^+$ current described in many preparations (20). Given the unusually high threshold of pituitary Na$^+$ channels (21), this shift would make nerve terminals much more sensitive to small depolarizations.

NO is known to bind soluble guanylate cyclase and stimulate production of cGMP (22), but NO still induced a persistent Na$^+$ current in nerve terminals treated with the guanylate cyclase inhibitor 6-phenylamino)-5,8-quinolinedione (20 µM, n = 4). In contrast, pretreatment with the sulfhydryl-alkylating reagent, N-ethylmaleimide (NEM), inhibited NO activation of persistent current in cardiac myocytes (Fig. 2, A and B). This suggests that the ultimate target of NO is a protein thiol, and this is consistent with the finding that the reducing agent dithiothreitol reverses NO-induction of persistent Na$^+$ current in hippocampal neurons (9).

When NO was applied to excised outside-out patches from nerve terminals, Na$^+$ channels became resistant to inactivation. In control experiments almost no Na$^+$ channel activity could be seen >20 ms after the start of a depolarizing pulse. After NO was applied, channel activity was high for the duration of the 50-ms pulse (Fig. 3A). Moreover, after NO application, sustained bursts of tetrodotoxin-sensitive Na$^+$ channel activity could be seen when patches were held at potentials more positive than −60 mV (Fig. 3B). NO treatment produced a significant increase in channel open probability well after control Na$^+$ current inactivated (Fig. 3C). The single-channel conductance of Na$^+$ channels was not altered by NO. A plot of single-channel current versus voltage gave a conductance of 18 pS for NO-modified Na$^+$ channels and data for control Na$^+$ channels superimposed along this line (Fig. 3D).

The activation of persistent Na$^+$ current in excised cell-free patches occurs in the absence of cGMP and further argues against a role for this second messenger. This finding together with the occlusion of this current by NEM in whole cell recordings (Fig. 2B) is consistent with a direct action of NO at a thiol group on either Na$^+$ channels themselves or on a closely associated membrane protein.

These results show that exogenously applied NO can activate persistent Na$^+$ current. However, whether this signaling pathway plays a role under physiological conditions is unclear, because the NO levels achieved by these exogenous NO application methods may not be physiologically relevant. To address this issue we tested whether persistent Na$^+$ current could be induced by endogenous NO production. To stimulate Ca$^{2+}$-dependent NOS activity in myocytes, we used the Ca$^{2+}$-ionophore, ionomycin, which has previously been shown to stimulate NO production in vascular smooth muscle (23). Using the NO-sensitive fluorophore, DAF-2 (19), we found that ionomycin increased NO production in myocytes. Fluorescence images produced by a confocal microscope showed that fluorescence intensity increased with time after ionomycin application and became very bright after 15 min. Fluorescence intensity averaged from several experiments was plotted to show the time course of this effect (Fig. 4B, triangles). The fluorescence in control untreated cells was relatively stable (Fig. 4B, circles). Thus, ionomycin produced a marked increase in NO synthesis beginning shortly following its addition. This increase in NO production was completely inhibited by pretreatment with the NOS inhibitor 7-nitroindazole (7-NI) (Fig. 4B, squares). The average fluorescence values were plotted for control, ionomycin, and ionomycin + 7-NI in Fig. 4C and show that ionomycin produces an ~7-fold increase in DAF-2 fluorescence after 25 min. The change induced by ionomycin was statistically significant, whereas the plot obtained for ionomycin application to 7-NI-treated cells was flat and statistically indistinguishable from the control plot. These experiments demonstrated that treatment ventricular myocytes with ionomycin increases cellular Ca$^{2+}$ to a level sufficient to activate NOS. The enhancement in NOS activity raises NO concentrations to levels that are readily detectable with DAF-2.

Because ionomycin treatment is an effective means of stimulating NOS, we used this method to determine whether endogenous NO can modify the activity of Na$^+$ channels in the same way as exogenous NO. Myocytes were treated with ionomycin as in Fig. 4 and voltage clamped 15–30 min later. After ionomycin treatment myocytes exhibited a ~3-fold increase ($n = 22, p < 0.001$) in persistent Na$^+$ current (measured at the end of a 200-ms pulse) compared with control cells ($n = 29$), and this increase was inhibited by pretreatment with 7-NI to inhibit NOS (Fig. 5). Similar results were obtained with another NOS inhibitor S-ethylisothiourea, and these results are summarized in Fig. 5B. 7-NI and S-ethylisothiourea failed to alter persistent Na$^+$ current on their own (Fig. 5B). Thus, production of NO enzymatically by NOS within ventricular myocytes can induce persistent Na$^+$ current.

**DISCUSSION**

This study has shown that NO modifies the activity of voltage-gated Na$^+$ channels in posterior pituitary nerve terminals and ventricular myocytes. This modification leads to the appearance of a persistent Na$^+$ current that fails to inactivate completely at depolarized membrane potentials. These two cell
types, peptidergic nerve terminals and heart muscle, normally express large transient Na$^+$ currents with little if any persistence. Application of NO either by the addition of NO donors or photolysis of caged NO induced the appearance of persistent Na$^+$ currents. NO donors have also been shown to increase persistent Na$^+$ current in hippocampal neurons (9), suggesting that this represents a general mechanism by which NO can modify electrical excitability.

Activation of persistent Na$^+$ current was independent of guanylate cyclase and was blocked by NEM treatment. Furthermore, NO produced the same modification of channel behavior in excised patches. These results suggest that a reactive nitrogen species interacts directly with the Na$^+$ channel or with a closely associated membrane protein. Several other channels are thought to be modulated by NO in the same way, including Ca$^{2+}$-activated K$^+$ channels (11, 14), cyclic nucleotide-gated channels (12), and ryanodine receptors (13). NO is thus capable of modulating the activity of a number of ion
channels, apparently through chemical modification of a protein thiol.

As the number of putative non-heme, S-nitrosylation targets of NO expands (15), the question of physiological relevance increases in importance. In the case of NO modification of the Ca\textsuperscript{2+}-activated K\textsuperscript{+} channel of vascular smooth muscle, it was shown that acetylcholine mimicked the action of exogenous NO (11), but the transduction pathway employed by acetylcholine to induce this effect was not clear. We stimulated NOS in cardiac myocytes by using ionomycin to elevate cytoplasmic Ca\textsuperscript{2+}. This produced a concomitant increase in the amplitude of persistent Na\textsuperscript{+} current. Both the NO rise and the modulation of Na\textsuperscript{+} channels were prevented by inhibitors of NOS. This experiment demonstrated that endogenous NO generated within a cell can modify the ion channels within its own plasma membrane. Thus, NO induction of persistent Na\textsuperscript{+} current can serve in physiological pathways for the modulation of membrane excitability.

Constitutive NOS is a Ca\textsuperscript{2+}/calmodulin activated enzyme found in neurons and muscle. In these excitable cells, NO induction of persistent Na\textsuperscript{+} current is likely to play an important role in regulating electrical activity. Altered inactivation behavior contributes to resurgent Na\textsuperscript{+} current, which has been shown to alter the capacity of synaptic inputs to generate action potentials (2). Persistent Na\textsuperscript{+} current generates voltage oscillations in cerebellar Purkinje cells (3). Exogenous NO can also generate voltage oscillations in putitary nerve terminals by inducing persistent Na\textsuperscript{+}, and this action would allow NO to act as a secretogogue (8). Modification of Na\textsuperscript{+} channels in nerve terminals can have a profound impact on presynaptic action potential shape, and this will dramatically alter Ca\textsuperscript{2+} entry and transmitter release (16). The induction of persistent Na\textsuperscript{+} current in synaptic nerve terminals could thus underlie some of the effects of NO on synaptic transmission and synaptic plasticity (22).

Constitutive NOS is linked to the cytoplasmic peripheral membrane protein syntrophin, as are brain and muscle Na\textsuperscript{+} channels (24). These interactions could bring NOS and Na\textsuperscript{+} channels into close proximity. Because NO is a labile signaling molecule, its production in close proximity to Na\textsuperscript{+} channels provides a potentially important mechanism for a selective action on this target. Cytoplasmic Ca\textsuperscript{2+} signals vary both spatially and temporally, and these variations can influence the signaling pathways that are activated (25, 26). Spatial variations in Ca\textsuperscript{2+} could determine the location where NO rises, and if channels are segregated, this will determine which channel types are modified.

This form of ion channel modulation is likely to be activated during physiological and pathological conditions associated with elevated intracellular Ca\textsuperscript{2+}. Variations in persistent Na\textsuperscript{+} current would have profound consequences for the spike patterns elicited by excitatory synaptic inputs (2), as well as spontaneous rhythmic activity in neurons (1). Such a mechanism may explain the fact that elevated Ca\textsuperscript{2+}, NO levels, and persistent Na\textsuperscript{+} current are found in the heart following hypoxia (6, 27–29) and in brain regions exhibiting epileptic activity (7) or following ischemic stroke (30).

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Induction of Persistent Sodium Current by Exogenous and Endogenous Nitric Oxide
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