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Ultraviolet Photoalteration of Late Na^+ Current in Guinea-pig Ventricular Myocytes

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Abstract. UV irradiation has multiple effects on mammalian cells, including modification of ion channel function. The present study was undertaken to investigate the response of membrane currents in guinea-pig ventricular myocytes to the type A (355, 380 nm) irradiation commonly used in Ca^{2+} imaging studies. Myocytes configured for whole-cell voltage clamp were generally held at −80 mV, dialyzed with K^+-, Na^+-free pipette solution, and bathed with K^+-free Tyrode's solution at 22°C. During experiments that lasted for ≈ 35 min, UVA irradiation caused a progressive increase in slowly-inactivating inward current elicited by 200-ms depolarizations from −80 to −40 mV, but had little effect on background current or on L-type Ca^{2+} current. Trials with depolarized holding potential, Ca^{2+} channel blockers, and tetrodotoxin (TTX) established that the current induced by irradiation was late (slowly-inactivating) Na^+ current (I_{Na}). The amplitude of the late inward current sensitive to 100 μM TTX was increased by 3.5-fold after 20–30 min of irradiation. UVA modulation of late I_{Na} may (i) interfere with imaging studies, and (ii) provide a paradigm for investigation of intracellular factors likely to influence slow inactivation of cardiac I_{Na}.

Key words: Ultraviolet irradiation — Tetrodotoxin — Na^+ current — Ca^{2+} current — Leak current

Introduction

UV irradiation has long been used as an experimental tool to modify membrane constituents in the investigation of cell excitability and Na^+ channel function. Early studies on amphibian nerve established that irradiation can increase threshold, depress action potential amplitude, and eventually block action potential generation (Audiat, Auger & Fessard, 1931; Booth, von Muralt & Stämpfli, 1950). Subsequent voltage-clamp studies on nerve axon and node of Ranvier demonstrated that the depressed excitability was due to pronounced block of Na^+ channels, with little or no change in channel selectivity or in the kinetics of the residual Na^+ current (I_{Na}) (Fox & Stämpfli, 1971; Fox, 1974; Oxford & Pooler, 1975; Conti, Cantu & Duclohier, 1988).

More recent studies on a variety of native and expressed channels indicate that UV irradiation can also activate/potentiate channel activity (Mendez & Penner, 1998; Leszkiewicz, Kandler & Aizenman, 2000; Chang, Xie & Weiss, 2001), and modify channel kinetics (Leszkiewicz et al., 2000; Middendorf & Aldrich, 2000). Wang and Wang (2002) investigated the effects of UV irradiation on human cardiac $Na_V1.5$ Na^+ channels expressed in HEK283t cells. Unlike the UV irradiation used in the studies on nerve Na^+ channels cited above (type C (190–290 nm) or B (290–320 nm)), Wang and Wang (2002) used UV type A (320–380 nm) light, and found that prolonged irradiation of the cells modified the gating of the expressed $Na_V1.5$ channels and eventually abolished channel activity.

In Ca^{2+} imaging studies on guinea-pig ventricular myocytes, we observed a progressive increase in the amplitude of slowly-decaying inward current elicited by 50-ms depolarizations. We surmised that the response was due to an action of UVA irradiation (alternate 355 and 380 nm) on slowly-inactivating (late, persistent) I_{Na}, a component of I_{Na} whose modification is implicated in the generation of arrhythmogenic afterdepolarizations (Ward & Giles, 1997; Maltsev et al., 1998) and linked to cardiac phenotypes that include long-QT syndromes, conduction dysfunction, and the Brugada syndrome (for review, *see* Tan et al., 2003). The objective of this study was to measure the effects of UVA irradiation

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on late I_{Na} and several other membrane currents in guinea-pig ventricular myocytes.

Materials and Methods

All procedures were carried out in accordance with national and university regulations on the care and treatment of laboratory animals. Guinea-pigs (250–300 g) were killed by cervical dislocation. Hearts were quickly excised, mounted on a Langendorff column, and perfused through the aorta with Ca^{2+}-free Tyrode's solution (37°C) that contained collagenase (0.08–0.12 mg/ml; Yakult Pharmaceutical Co., Tokyo, Japan) for 10–15 min. The cells were dispersed and kept in a storage solution (22°C) that contained (mM) KOH 80, KCl 30, KH_2PO_4 30, $MgSO_4$ 3, glutamic acid 50, taurine 20, glucose 20, ethylene glycol-bis(b-aminoethyl)-N,N,N,N-tetraacetic acid (EGTA) 0.5, and *N*′-2-hydroxyethylpiperazine-*N*′-2-ethanesulphonic acid (HEPES) 10 (pH 7.4 with KOH).

A few drops of the cell suspension were placed in a 0.3-ml perfusion chamber mounted on an inverted microscope stage. Whole-cell membrane currents were recorded using an EPC-9 amplifier (HEKA Electronics, Mahone Bay, NS, Canada). Recording pipettes were fabricated from thick-walled borosilicate glass capillaries (H15/10/137, Jencons Scientific Ltd., Leighton Buzzard, UK), and had resistances of 1.5–2.5 MΩ when filled with pipette solution. The series resistance ranged between 3 and 7 MΩ, and was compensated by 60–80%. Current signals were low-pass filtered at 3 kHz, and digitized with an A/D converter (Digidata 1200A, Axon Instruments, Foster City, CA) and pCLAMP software (Axon Instruments) at a sampling rate of 8 kHz.

Tyrode's solution contained (mM) NaCl 143, KCl 5.4, $CaCl_2$ 1.8, $MgCl_2$ 1.2, glucose 10, and HEPES 5 (pH 7.4 with NaOH). The Ca^{2+}-free solution used for enzymatic dissociation was made by omitting $CaCl_2$, and the K^+-free solution used to bathe myocytes in the experiments was made by replacing KCl with CsCl. K^+-free pipette solution contained (mM) 50 CsCl, 110 Cs-aspartate, 10 HEPES, 10 BAPTA, 4.8 MgATP, and 3.2 $CaCl_2$ (pH 7.3 with CsOH) (pCa 7). In some experiments, free Ca^{2+} in the pipette solution was lowered to < 1 nM by replacement of BAPTA/Ca^{2+} with 40 mM EGTA. Tetrodotoxin (Alomone Labs, Jerusalem, Israel) and $NiCl_2$ were directly dissolved in superfusates. Nifedipine (Sigma Chemical, St. Louis, MO) and ryanodine (Sigma) were prepared as stock solutions in dimethyl sulfoxide and water, respectively.

The light source used to irradiate the cells was a 75 watt xenon lamp in a PTI Deltascan-4000 ratio fluorescence system (Photon Technology Internat., South Brunswick, NJ). The cells were alternately irradiated by bands of light with peaks at 355 nm and 380 nm. Experiments were conducted at 22–23°C, and the results are expressed as means ± SEM. Comparisons were made using Student's *t*-test, and differences were considered significant when $P < 0.05$.

Results

Slowly-inactivating I_{Na} at −40 mV

The records of membrane currents in Fig. 1*A* illustrate that 500-ms depolarizations from −80 to −40 mV elicited large rapidly-activating inward currents that first decayed rapidly and then much more slowly. These currents were sensitive to 100 μM TTX, and measurements of the difference current (control minus TTX) during depolarization indicate that late I_{Na} declined from −1 ± 0.2 pA/pF at 25 ms, to −0.5 ± 0.1 pA/pF at 200 ms and −0.4 ± 0.1 pA/pF at 500 ms ($n = 9$ myocytes) (Fig. 1*B*). The latter two values are in good agreement with those obtained by others on ventricular myocytes depolarized to ≈ −40 mV for 200–350 ms (range −0.23 ± 0.02 to −0.75 ± 0.1 pA/pF) (Maltsev et al., 1998; Ahern et al., 2000; Sakmann et al., 2000; Zygmunt et al., 2001).

Effects of Irradiation on Membrane Currents

Figure 2 shows records of membrane currents obtained at post-patch times of 5, 15, and 30 min from representative control and irradiated myocytes. The myocytes were held at −80 mV, and depolarized with a double-pulse (200 ms to −40 mV, 50 ms to +10 mV) every 30 s. In the control myocyte, the pulse step to −40 mV at 5 min post-patch elicited a typical multiphasic I_{Na} (Maltsev et al., 1998; Sakmann et al., 2000), and the second step to +10 mV for 50 ms elicited inward $I_{Ca,L}$ (Fig. 2*A*). Late I_{Na} was stable during the 30-min observation time, whereas $I_{Ca,L}$ underwent a gradual rundown.

In the irradiated myocyte, there was a progressive increase in the slowly-decaying phase of the inward current at −40 mV (Fig. 2*B*). This was not due to a marked deterioration of the myocyte because neither the holding current at −80 mV nor $I_{Ca,L}$ at +10 mV was adversely affected by the irradiation (Fig. 2*B*, *C*). As a point of reference, 59 of 75 myocytes that were irradiated remained "healthy" for > 25 min; the other 16 developed leak problems within 5 min and were not investigated further.

Identity of the Irradiation-induced Current

It seemed likely that the increase in late inward current at −40 mV caused by irradiation was primarily due to an increase in slowly-inactivating I_{Na}. To establish this point, we conducted three sets of experiments. In the first, we moved the holding potential from −80 to −40 mV for 2-min test periods to inactivate Na^+ channels, and measured the holding current (−40 mV). We found that irradiation had little effect on the magnitude of the holding current; in six irradiated myocytes, it was −0.3 ± 0.1 pA/pF during test periods at early times (5–10 min post-patch), and a similar −0.4 ± 0.1 pA/pF during test periods at late times (≈ 30 min post-patch) (Fig. 3*A*, *B*). At non-test times, the myocytes were depolarized from −80 to −40 mV for 200 ms to elicit I_{Na}, and the magnitude of the inward current measured at 25 ms depolarization increased from −1.4 ± 0.1 pA/pF (5 min post-patch) to −4.1 ± 0.4 pA/pF (30-min post-patch) ($P < 0.001$). In the second series of experiments, we found that neither 5–10 μM nifedipine ($n = 10$) nor 50 μM Ni^{2+}

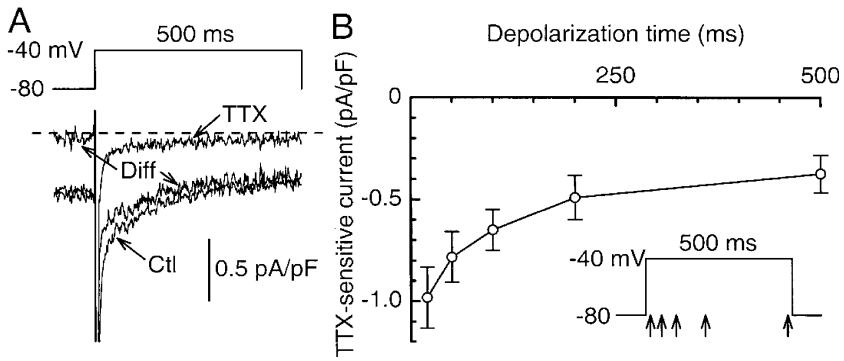

Fig. 1. Slowly-inactivating I_{Na} in guinea-pig ventricular myocytes. (*A*) Slowly-inactivating inward currents elicited by depolarizations from −80 to −40 mV before (*Ctl*) and 4 min after the addition of 100 μM TTX. The control records were taken at 10 min post-patch breakthrough. Also shown is the difference current (*Diff*) obtained by subtraction of the TTX record from the control record. The dashed line here and in other records indicates the zero-current level. Fast I_{Na} (truncated here) was poorly controlled under the conditions employed (high (143 mM) external Na^+), and residual fast I_{Na} of ≈ 3 pA/pF was always evident in the presence of 100 μM TTX (also *see* Fig. 4*A*). The latter result is not surprising because previous studies have determined that under high external Na^+ conditions the K_D for block of fast I_{Na} by TTX is ≥ 5 μM (Antoni, Bocker & Eickhorn, 1988; Schneider et al., 1994; Maier et al., 2002). (*B*) Time course of decay of the TTX-sensitive current; $n = 9$ myocytes.

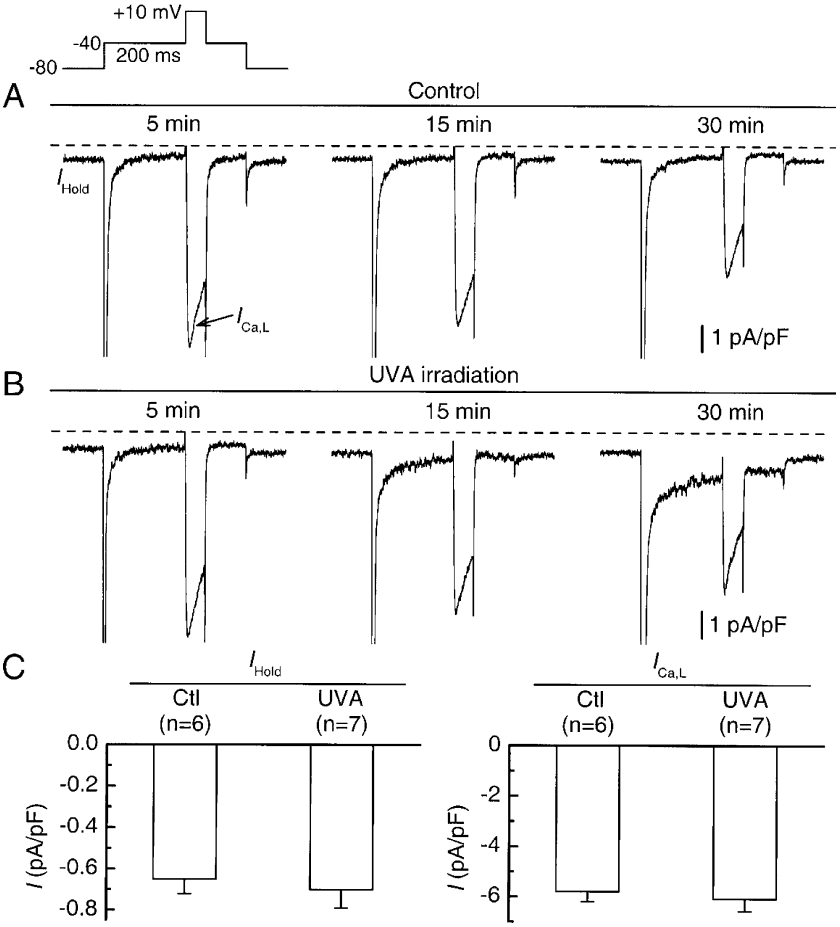

Fig. 2. Effect of UVA irradiation on membrane currents in myocytes depolarized from −80 to −40 mV, and then to +10 mV. (*A*) Records from a representative control myocyte showing stable holding current at −80 mV (I_{Hold}), stable inward transient at −40 mV, and typical rundown of $I_{Ca,L}$ at +10 mV during lengthy experiments. The times here and in subsequent panels refer to post-patch times. (*B*) Records obtained from a representative irradiated myocyte. I_{Hold} remained stable throughout the experiment, and the rundown of $I_{Ca,L}$ was not excessive. However, there was a marked, progressive increase in the late inward current at −40 mV. (*C*) Comparison of the amplitudes of I_{Hold} and peak $I_{Ca,L}$ measured in control (*Ctl*) and UVA-irradiated myocytes at 25 min post-patch (reference: zero current).

($n = 3$), blockers of L-type and T-type channels, respectively (McDonald et al., 1994; Pascarel, Brette & Le Guennec, 2001), had a significant effect on the enhanced inward current in irradiated myocytes (*data not shown*). In the final series, we found that applications of 100 μM TTX reversibly blocked the irradiation-induced current (Fig. 3*C*) (*see* also below).

An alternative explanation for the findings with TTX is that the irradiation-induced inward current was not late I_{Na}, but rather an inward current that

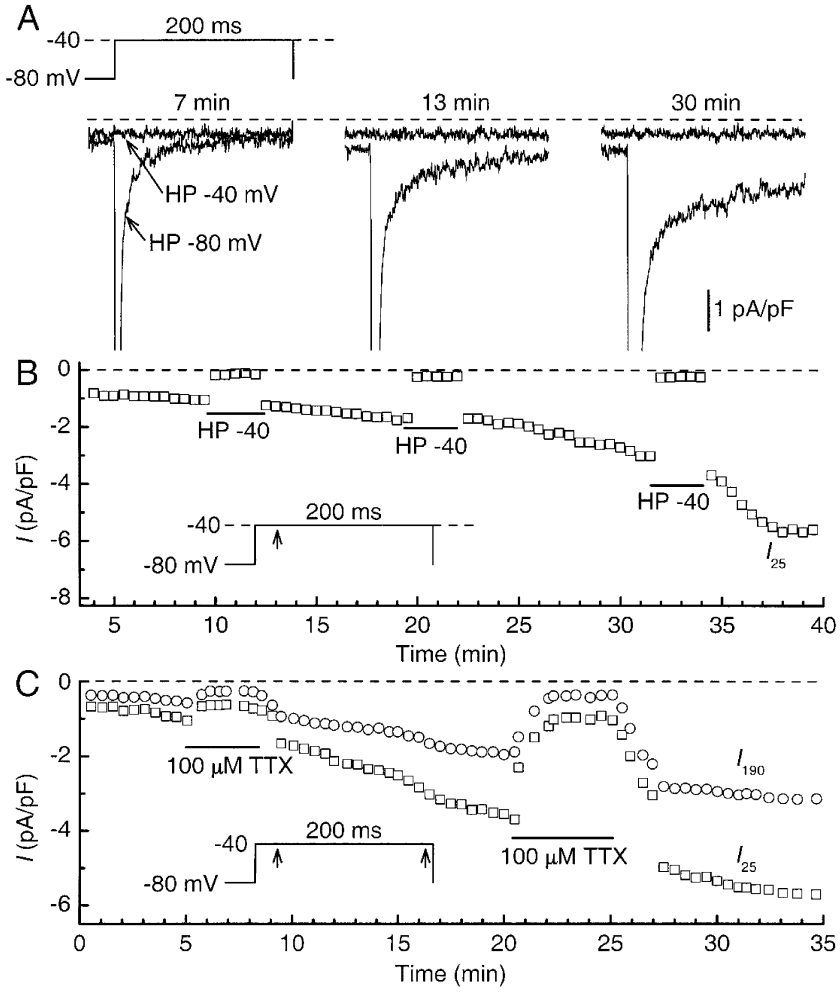

Fig. 3. Sensitivity of late inward current (−40 mV) in irradiated myocytes to changes in holding potential and 100 μM TTX. (*A, B*) Data obtained from two representative myocytes that were held at −80 mV and depolarized to −40 mV for 200 ms every 30 s except for three 2-min quiescent test periods at a holding potential (HP) of −40 mV. In *A*, records obtained just before and at the end of each test period are superimposed. The times refer to onsets of test periods. *B* is a timeplot of the magnitude of the average current at −40 mV measured over the 22–28 ms (i.e., I_{25}) interval during 200-ms depolarizations from −80 mV, or a 6-ms interval every 30 s during test periods at holding potential −40 mV. (*C*) Effect of 100 μM TTX on I_{25} and I_{190} (average current between 180 and 200 ms) in a representative myocyte.

was dependent on prior large influx of Na^+ into subsarcolemmal regions near Na^+ channels. However, this possibility seems unlikely because any current induced as a consequence of fast I_{Na} (for example, Na^+-Ca^{2+} exchanger current) would have been outward in direction (e.g., *see* Su et al., 2001), unless depolarization had also caused a marked increase in intracellular Ca^{2+} concentration due to release of Ca^{2+} from the sarcoplasmic reticulum. The latter is unlikely to have occurred in the irradiated myocytes in view of the stability of $I_{Ca,L}$, and the lack of effect of pretreatment with 1 μM ryanodine ($n = 4$). In addition, the irradiated myocytes did not display a telltale large inward Na^+-Ca^{2+} exchanger current on repolarization to −80 mV after a pulse of $I_{Ca,L}$ (*see* Fig. 2*B*), and development of large late I_{Na} was also observed in myocytes that were dialyzed with 40 mM EGTA pipette solution ($n = 3$).

Summary of TTX Data

The set of records in Fig. 4*A* illustrates several features of TTX action on irradiated myocytes. The top row shows block of the irradiation-enhanced late inward current, as well as the small spike of I_{Na} that remained in the presence of the toxin (also *see* the legend to Fig. 1). The second row of records illustrates that TTX had no effect on membrane current elicited at high positive potentials where late I_{Na} is expected to be very small.

TTX-sensitive current (control minus 100 μM TTX) was analyzed in control ($n = 19$) and irradiated ($n = 18$) myocytes that were exposed to the toxin at ≈ 25 min post-patch. Current density was measured at two times (25, 190 ms) during 200-ms depolarizations to −40 mV (I_{25}, I_{190}), and the results are summarized in Fig. 4*B*. In the control myocytes, the I_{25} and I_{190} values were −0.91 ± 0.11 and −0.51 ± 0.04 pA/pF, respectively; in the irradiated myocytes, these densities were about 3.5-fold larger ($P < 0.001$). By contrast, the non-blocked spike of I_{Na} was relatively insensitive to the prolonged irradiation (Fig. 4*C*).

Discussion

UVA irradiation caused a marked increase in the amplitude of the slowly-inactivating component of

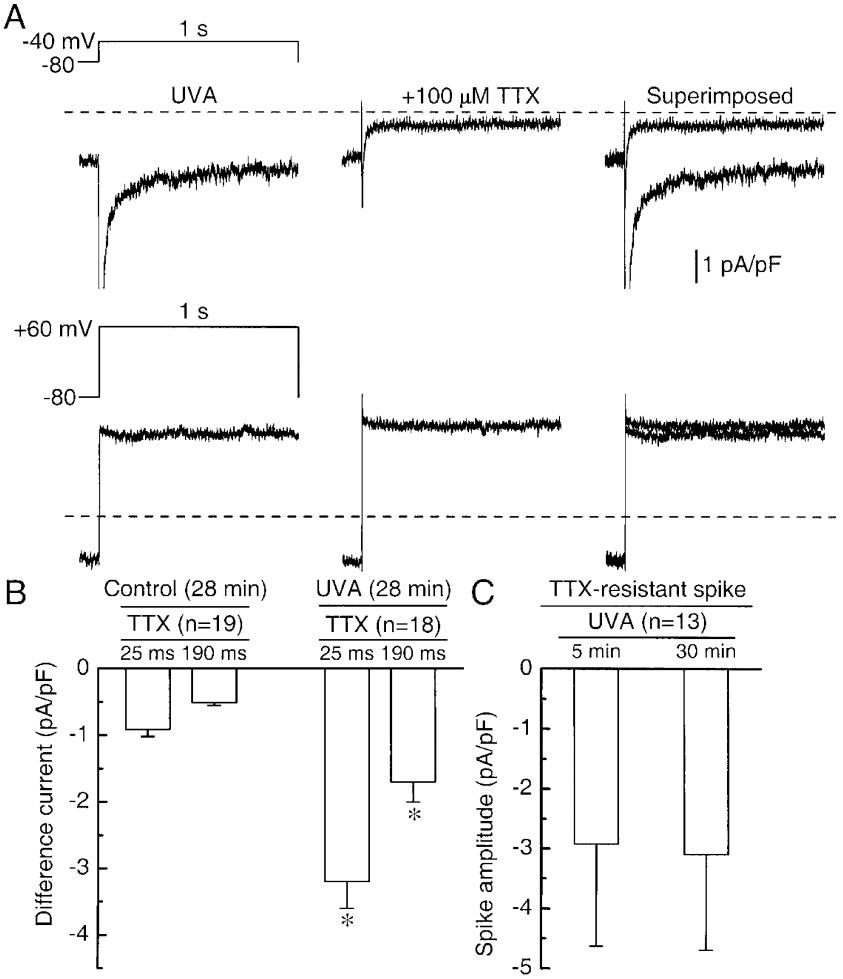

Fig. 4. Effects of TTX on membrane currents in control and irradiated myocytes. (*A*) Effects of TTX on membrane currents in a myocyte irradiated for 27 min. The currents were recorded on depolarizations to −40 mV (*top row*) and +60 mV (*bottom row*). Note the TTX block of late I_{Na} and the presence of a residual I_{Na} spike at −40 mV, as well as the lack of effect of TTX on membrane current at +60 mV. (*B*) TTX-sensitive current measured after 25 and 190 ms depolarization from −80 to −40 mV. The TTX was applied at ≈ 25 min post-patch. $^*P < 0.001$ versus control. (*C*) Lack of effect of irradiation on the non-blocked spike of I_{Na} at −40 mV measured during exposures to 100 μM TTX after 5 and 30 min of irradiation.

inward current elicited by depolarizations from −80 to −40 mV. This component was identified as late I_{Na} because it was fully inactivated at depolarized holding potential, insensitive to nifedipine and Ni^{2+}, and suppressed by TTX. To our knowledge, this is the first account of UV modulation of slowly-inactivating I_{Na} in cardiac cells. The pronounced effect of irradiation on late I_{Na} was in marked contrast to its lack of effect on the TTX-suppressed Na^+ spike elicited on depolarization to −40 mV, $I_{Ca,L}$ elicited on depolarizations to +10 mV, and background current at holding potential −80 mV. The lack of effect on holding current contrasts with findings of progressive activation of very large leak currents during irradiation of mammalian cell lines (Mendez & Penner, 1998; Wang & Wang, 2002) and *Xenopus* oocytes (Middendorf, Aldrich & Baylor, 2000). That irradiation can have relatively selective effects on membrane currents has previously been demonstrated by Chang et al. (2001) who found that UVA light potentiated current mediated by $GABA_A$ receptors, but not current mediated by $GABA_C$ receptors.

To our knowledge, this is only the second account of the effects of UV irradiation on membrane currents in cardiac myocytes (*see* Nathan, Pooler & DeHaan, 1976), and the first to demonstrate pronounced changes in late I_{Na}. However, Wang and Wang (2002) have investigated the effects of UVA light on current carried by human cardiac $Na_V1.5$ α-subunits expressed in HEK293 cells. The currents inactivated with a monoexponential time course, and irradiation for 10 min increased the time constant at −40 mV from ≈ 2 ms to ≈ 5 ms. Irradiation also reduced the amplitude of the current, such that little current remained after 20 min treatment; however, comparative data on current amplitude in control cells were not provided. Wang and Wang (2002) also observed that UVA irradiation caused development of a "maintained" current during step depolarizations; the maintained current reached a quasi-steady-state level within 5 to 7 min of the onset of irradiation. In their study, the term "maintained" referred to current at the end of 8-ms depolarizations. In the present study, we found that any maintained (i.e., non-inactivating) I_{Na} present after 2-min depolarization (shift in holding potential) to −40 mV was not significantly affected by prolonged irradiation (Fig. 3*A*). Evidently,

irradiation slowed but did not prevent entry of Na^+ channels into the inactivated state.

In earlier studies on nerve cells (Fox, 1974; Oxford & Pooler, 1975; Conti et al., 1988) and embryonic chick heart cell aggregates (Nathan et al., 1976), block of Na^+ channels was dependent on the wavelength of the irradiation, with a sharp optimum near 280 nm where absorption by (channel) proteins is particularly strong due to the contribution of aromatic amino acids such as tryptophan (Wetlaufer, 1962; Jones, Hayon & Busath, 1986; Middendorf & Aldrich, 2000). In view of the much longer wavelengths employed in the present study, it is improbable that the irradiation directly modified tryptophan residues. More likely, the modification of late I_{Na} by UVA irradiation was caused by the generation of reactive oxygen species (ROS) (Morliere et al., 1991; Devary et al., 1992; Bender et al., 1997; Klotz, Briviba & Sies, 1997; Mendez & Penner, 1998; Huang et al., 2001). In that regard, the application of H_2O_2 has been shown to cause TTX-sensitive lengthening of the ventricular action potential (Beresewicz & Horackova, 1991; Ward & Giles, 1997), most likely by activating protein kinase C (Ward & Moffat, 1995) with resultant slowing of Na^+ channel inactivation (Qu et al., 1994; Ward & Giles, 1997; Watson & Gold, 1997). However, the changes in late I_{Na} found in the latter studies were moderate compared to those found here, and late I_{Na} was actually suppressed by H_2O_2 in one extensive study on the subject (Barrington, Martin & Zhang, 1997). A second possible mediator of the effects of UVA light on I_{Na} is nitric oxide (NO). UVA irradiation enhanced the formation of NO in cardiac (Combes et al., 2001) and smooth muscle (Andrews, McGuire & Triggle, 2003) myocytes, and the generation of NO has been shown to induce marked increases in the late I_{Na} of rat ventricular myocytes (Ahern et al., 2000).

UVA-induced ROS can also mediate activation of membrane-associated Src tyrosine kinase, inhibition of phosphotyrosyl phosphatase, tyrosine phosphorylation of growth factor receptors, and activation of downstream kinases (Devary et al., 1992; Warmuth et al., 1994; Aikawa et al., 1997; Bender et al., 1997; Huang et al., 2001; Katiyar, 2001). The pertinence of such actions to the modification of late I_{Na} in irradiated myocytes will require careful investigation, with due account of recent results suggesting that an increase in tyrosine phosphorylation may inhibit fast I_{Na} in nerve cells (Hilborn, Vaillancourt & Rane, 1998; Ratcliffe et al., 2000), but possibly not in ventricular myocytes (Wang et al., 2003).

Independent of the intermediate steps involved in the modulation of late I_{Na} by irradiation, the final step involves modification of a channel site or sites. The best known modification that increases late I_{Na} is that caused by the binding of lipophilic compounds (e.g., batrachotoxin, veratridine, aconitine) to receptor site-2 in Na^+ channels (Honerjäger, 1982; Nilius, Boldt & Benndorf, 1986; Wright, 2002). However, a hallmark feature of site-2 action, large slow tails of inward I_{Na} on repolarization to ≈ -80 mV (Huang, Yatani & Brown, 1987; Zong, Dugas & Honerjäger, 1992; Cole et al., 1997), was not evident in irradiated myocytes (Fig. 2*B*). Cormier et al. (2002) have recently reported that truncation of the C-terminus of the cardiac $hNa_V1.5$ channel increased the density of current at the end of 150-ms depolarizations by about 5-fold. Thus, it is possible that the final step in the modulation of late I_{Na} by irradiation involves antagonism of the inactivation-promoting interaction between the C-terminus and the channel pore.

In summary, we have shown that the UVA irradiation typically used in Ca^{2+} imaging studies has pronounced effects on late I_{Na} in guinea-pig ventricular myocytes. Depending on the experimental protocols used in such studies, the irradiation-modified influx of Na^+ may perturb the cellular processes under investigation.

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