Inhibition of Neuronal Na\(^+\) Channels by Antidepressant Drugs\(^1\)

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**ABSTRACT**

Although tricyclic antidepressant (TCA) blockade of cardiac Na\(^+\) channels is appreciated, actions on neuronal Na\(^+\) channels are less clear. Therefore, the effects of TCAs (amitriptyline, doxepin and desipramine) as well as trazadone and fluoxetine on voltage-gated Na\(^+\) current (I\(_{\text{Na}}\)) were examined in bovine adrenal chromaffin cells using the whole-cell patch-clamp method. Amitriptyline produced concentration-dependent depression of peak I\(_{\text{Na}}\) evoked from a holding potential of -80 mV with \(K_D\) value of 20.2 \(\mu\)M and a Hill coefficient of 1.2. Although 20 \(\mu\)M amitriptyline induced no change in the rate or voltage dependence of I\(_{\text{Na}}\) activation, steady-state inactivation demonstrated a 15-mV hyperpolarizing shift. Similar results were observed for doxepin and desipramine. This shift in steady-state inactivation was associated with a slowed rate of recovery from the inactivated state. Contrasting results were observed with the atypical antidepressants: while 20 \(\mu\)M fluoxetine depressed peak I\(_{\text{Na}}\) by 61% and caused a 7-mV hyperpolarizing shift in steady-state inactivation, 100 \(\mu\)M trazadone decreased peak I\(_{\text{Na}}\) by only 19% and caused only a 3-mV shift. Although the magnitude of fluoxetine effects was similar to those of the TCAs, the onset of fluoxetine effects was substantially slower than for amitriptyline. In voltage-clamp and current-clamp measurements from neonatal rat dorsal root ganglion neurons, 2 \(\mu\)M amitriptyline decreased I\(_{\text{Na}}\) by 52% and depressed action potential dynamics consistent with enhanced Na\(^+\) channel inactivation. The effects of the TCAs on I\(_{\text{Na}}\) are similar to local anesthetic behavior and could contribute to certain analgesic actions.

**Methods**

Bovine adrenal chromaffin cells were generously supplied by Dr. Y. I. Kim (Department of Biomedical Engineering, University of Virginia, Charlottesville, VA) and were isolated according to a previously reported method (Greenberg and Zinder, 1982) with modifications (Creutz et al., 1987). Neonatal (P8-P12) rat DRG neurons were isolated by a method modified from McLean et al. (1988). Briefly, after dissection from the perispinal tissue, ganglia were minced and incubated in 2.5 mg/ml trypsin (Sigma Chemical, St. Louis, MO) supplemented with 2 mg/ml type I collagenase (Sigma Chemical) for 30 min at 37°C. Cells were triturated five to eight times and resuspended in Dulbecco’s modified Eagle’s medium

**ABBREVIATIONS:** AP, action potential; CSF, cerebrospinal fluid; DRG, dorsal root ganglion; dV/dt\(_{\text{max}}\), maximum rate of depolarization; I\(_{\text{Na}}\), sodium current; I-V, current voltage; V\(_{\text{H}}\), holding potential; LA, local anesthetic; EGTA, ethylene glycol bis(\(\beta\)-aminoethyl ether)-N,N,N’,N’-tetraacetic acid; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; TCA, tricyclic antidepressant.
(GIBCO BRL, Gaithersburg, MD) with 10% fetal calf serum (HyClone Laboratories, Logan, UT), 50 U/ml penicillin and 50 μg/ml streptomycin (Sigma Chemical). Cells were plated onto poly-l-lysine-coated glass coverslips and maintained in an incubator at 37°C in 5% CO2/95% air. Best results for voltage-clamp experiments were obtained from cells within 2 days of isolation, before extensive processes developed.

For measurement of INa in bovine adrenal chromaffin cells, the external bathing solution contained (in mM) 141 NaCl, 5 KCl, 0.2 CaCl₂, 1 CoCl₂, 1 MgCl₂ and 10 HEPES, adjusted to pH 7.4 with 1 M NaOH. The patch pipette solution contained (in mM) 120 CsCl, 20 tetraethylammonium chloride, 1 CaCl₂, 11 EGTA-CsOH, 11 HEPES and 5 MgATP, adjusted to pH 7.3 with 1 M HCl. For voltage-clamp measurements from DRG neurons, the external recording solution contained (in mM) 10 or 30 NaCl, 130 or 150 tetraethylammonium chloride, 1 MgCl₂, 0.2 CaCl₂, 1 CoCl₂, and 10 HEPES, adjusted to pH 7.4 with 1 M CsOH. The patch pipette solution for these experiments contained (in mM) 100 CsCl, 2.5 MgCl₂, 10 EGTA, 30 CsOH, 40 HEPES, 2 MgATP and 0.3 NaGTP, adjusted to pH 7.3 with 1 M HCl. For current clamp measurements (fig. 1A) within 30 sec of drug application. In the presence of 20 M amitriptyline, peak INa fell by 51 ± 2% (mean ± S.E.M., n = 13 cells). The time to peak (tp) of INa was not affected by antidepressant treatment; for example, tp at 0 mV under control conditions and in the presence of amitriptyline was 1.3 ± 0.1 and 1.2 ± 0.1 msec (n = 5), respectively. Figure 1B summarizes the peak INa triggered by test potentials ranging from −50 to +60 mV from a holding potential of −80 mV under control, 20 M amitriptyline-treated and recovery conditions. Although there appeared to be no obvious shift in the voltage dependence of activation based on the I/V relation, steady-state activation was estimated by calculation of the peak conductance, GNa(V), at each test potential, V, according to Ohm’s law:

\[ G_{Na}(V) = \frac{I_{Na}}{V - E_{Na}} \]

where ENa, the apparent reversal potential based on the I/V curve. GNa(V) was then fit to the Boltzmann function, which under control conditions yielded \( k_n = 6.3 ± 0.5 \text{ mV} \) (n = 10) and \( V_n = −9.1 ± 3.0 \text{ mV} \). Amitriptyline altered neither \( k_n \) nor \( V_n \), suggesting a lack of effect on the voltage dependence of Na⁺ channel activation.

The suppression of INa by amitriptyline was concentration-dependent and also characteristic of the TCAs doxepin, desipramine and nortriptyline (fig. 2). The concentration dependence of amitriptyline-induced blockade was fitted to a logistic equation:

\[ I_{Na} = I_{Na,control} \cdot \left[ 1 + \left( \frac{|D|}{K_D} \right)^{nH} \right]^{-1} \]

where \( V_n \) is the potential when \( f(V) \) is equal to 0.5 and \( k_n \) is the slope factor.

Where appropriate, data are presented as mean percentage of control ± S.E.M. and the number of cells tested (n). The rates of recovery from inactivation and the onset of use-dependent blockade were fit to exponential equations using Sigmaplot. For the analysis of concentration-dependence and rate of recovery from inactivation, standard errors derived from the fitted data were used to test for significant differences. Statistical significance of a drug effect was determined using paired Student’s t test with P < .05 considered significant.

**Results**

As initially reported by Fenwick et al. (1982), bovine adrenal chromaffin cells express a rapidly activating and inactivating INa, which in our experiments reached a peak of 845 ± 450 pA (mean ± S.D., n = 54) in response to a step depolarization of −10 to +10 mV from a holding potential of −80 mV. The addition of amitriptyline to the bathing solution induced a marked decrease in INa over a range of test potentials (fig. 1A) within 30 sec of drug application. In the presence of 20 M amitriptyline, peak INa fell by 51 ± 2% (mean ± S.E.M., n = 13 cells). The time to peak (tp) of INa was not affected by antidepressant treatment; for example, tp at 0 mV under control conditions and in the presence of amitriptyline was 1.3 ± 0.1 and 1.2 ± 0.1 msec (n = 5), respectively. Figure 1B summarizes the peak INa triggered by test potentials ranging from −50 to +60 mV from a holding potential of −80 mV under control, 20 M amitriptyline-treated and recovery conditions. Although there appeared to be no obvious shift in the voltage dependence of activation based on the I/V relation, steady-state activation was estimated by calculation of the peak conductance, GNa(V), at each test potential, V, according to Ohm’s law:

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**Fig. 1.** Inhibition of INa from a representative bovine adrenal chromaffin cell by the TCA amitriptyline. A, INa waveforms shown were elicited by step potentials to −20, −10 and 0 mV from a holding potential of −80 mV. The dotted lines indicate the zero transmembrane current level. B, Peak INa as a function of test potential indicates no obvious shift in the voltage-dependent activation with the application of 20 M amitriptyline.
where $K_D$ is the concentration for half-maximal blockade, $[D]$ is the drug concentration and $n_H$ is the slope factor (or Hill coefficient). For amitriptyline, $K_D$ and $n_H$ were estimated to be 20.2 $\mu$M and 1.2, respectively, consistent with the notion of a single binding site. Although the suppression of $I_{Na}$ was a shared property of the TCAs examined, the atypical antidepressants trazodone and fluoxetine differed in their ability to inhibit $I_{Na}$. Trazodone (100 $\mu$M) induced only a minor blockade of $I_{Na}$ to 80 ± 2% ($n = 4$) of control (fig. 3A). In contrast, 20 $\mu$M fluoxetine reversibly depressed $I_{Na}$ to 38 ± 4% ($n = 5$) of control (fig. 3B), a level comparable to that induced by amitriptyline, while the onset of $I_{Na}$ blockade was somewhat slower than that of amitriptyline and the other TCAs. Figure 4 illustrates the comparative time course of amitriptyline and fluoxetine-induced blockade on $I_{Na}$ measured from the same chromaffin cell. Cells were repetitively pulsed from -80 to 0 mV every 4 sec, a rate slow enough to permit complete recovery from inactivation (determined by pilot studies) but fast enough to allow resolution of onset and recovery from blockade. Both phases were well described by a single exponential decay function with on and off time constants $\tau_{ON}$ and $\tau_{OFF}$, respectively. For 20 $\mu$M amitriptyline, $\tau_{ON}$ was 16 ± 3 sec ($n = 4$), and $\tau_{OFF}$ was 26 ± 4 sec. In contrast, the time course for blockade with 20 $\mu$M fluoxetine was significantly slower: $\tau_{ON}$ was 126 ± 24 sec ($n = 4$) and $\tau_{OFF}$ was 54 ± 7 sec. Unlike amitriptyline, the onset of $I_{Na}$ suppression was preceded by a delay of 45 ± 13 sec ($n = 4$), while recovery began immediately on removal of fluoxetine from the recording chamber.

Time-dependent Na⁺ channel inactivation was assessed by fitting the inactivating phase of $I_{Na}$ to a single exponential decay function of time, $I_{Na,t} = A_0 \exp(-t/\tau_{INa,t})$, where $A_0$ is the current amplitude and $\tau_{INa,t}$ is the time constant of inactivation.

Amitriptyline (20 $\mu$M) had no effect on the time course of inactivation for test potentials ranging from -10 to +40 mV. For example, $\tau_{INa,t}$ was 1.5 ± 0.2 and 1.4 ± 0.2 msec ($n = 5$) under control and amitriptyline-treated conditions, respectively, in response to a voltage step to 0 mV. Although the TCAs did not change the inactivation rate, steady-state inactivation was markedly altered (fig. 5A). To estimate steady-state inactivation, peak $I_{Na}$ was triggered by a test pulse to 0 mV from prepulse potentials, 5 sec in duration, from -95 to +40 mV. For one set of experiments, data were normalized and fit to the Boltzmann function, yielding control values for $k_0$, -6 ± 1 mV ($n = 5$) and for $V_n$ of -58 ± 2 mV. Amitriptyline (20 $\mu$M) shifted $V_n$ toward hyperpolarized potentials by 15 ± 1 mV ($n = 5$), while it exerted no observable effect on $k_0$. This effect was readily reversible and concentration dependent (fig. 5B). To gain further insight into the mechanisms of amitriptyline-induced blockade of $I_{Na}$, the rate of recovery from inactivation was examined. This was accomplished using two voltage steps to +10 mV separated by a repolarizing interpulse to -80 mV for durations ranging from 120 msec to 6 sec. Recovery from inactivation was estimated by the ratio of peak $I_{Na}$ evoked by the second pulse ($I_{Na,2}$) to peak $I_{Na}$ triggered by the initial pulse ($I_{Na,1}$). The results plotted in figure 5 show that amitriptyline delayed recovery of a major fraction of $I_{Na}$ from inactivation. Under both control and amitriptyline-treated conditions, $I_{Na,2}/I_{Na,1}$ was well fit as a biexponential process:

$$I_{Na,2}/I_{Na,1} = A_P \cdot \exp(-t/\tau_{RP}) + A_S \cdot \exp(-t/\tau_{RS})$$

where $A_P$ and $\tau_{RP}$ are the amplitude and time constant for a fast component, and $A_S$ and $\tau_{RS}$ are the amplitude and time constant for a slow component. As shown in figure 6, 10 $\mu$M amitriptyline markedly increased $\tau_{RS}$ by ~10-fold. To assess this in another manner, depression of the peak $I_{Na}$ by amitriptyline would be reflected in a delay of the recovery time constant, $\tau_{RS}$, to a value of $\tau_{RS}^*$ by the following equation:

$$\tau_{RS}^* = \frac{\tau_{RS} \cdot A_P}{A_P + A_S} \cdot \tau_{RS}$$

$$AF = \frac{A_P}{A_S + A_P}$$

where $AF$ is the recovery factor, $A_P$ the amplitude of the fast component of recovery, and $A_S$ the amplitude of the slow component. The results plotted in figure 6 show that amitriptyline markedly increased $\tau_{RS}$ by ~10-fold. To assess this in another manner, depression of the peak $I_{Na}$ by amitriptyline would be reflected in a delay of the recovery time constant, $\tau_{RS}$, to a value of $\tau_{RS}^*$ by the following equation:

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considered negligible at 0 mV. For each cell, the peak INa triggered after corrected for leak and capacitive artifact; instead, leakage current was mV for 5 sec before evoking a test pulse to 0 mV. Currents were not Chromaffin cells were held at a prepulse voltage ranging from an exponential function of the number of depolarizations each prepulse voltage was normalized to the peak I Na and fit to the Boltzmann function with parameters describing the voltage for half steady-state inactivation, Vn, and the slope factor, kn. A, Steady-state inactivation from a cell before (∙∙∙) and after recovery (∙∙∙). B, Concentration-dependence of amitriptyline of the shift in Vn, and effect of 20 μM concentration of the other drugs examined.

Amitriptyline was estimated using lower holding potentials (VH) in which more channels would be inactivated. For VH of −70, −60 and −50 mV, the EC50 was estimated to be 14, 7 and 3 μM amitriptyline. To verify Na+ channel inhibition in the DRG neurons by amitriptyline, voltage-clamp measurements were taken using an external recording solution with the Na+ concentration decreased from 141 mM to 10 or 30 mM to ensure suitable clamp conditions. DRG neurons can express two types of Na+ channels (Roy and Narahashi, 1992), which may account for the differential response of neurons to sustained depolarizing current injections under current-clamp conditions (Elliott and Elliott, 1993). As shown in figure 7, both slow and fast INa, measured from two different neurons, appeared to exhibit a similar range of sensitivity to amitriptyline. Overall, DRG peak INa fell to 48 ± 4% of the control amplitude with application of 20 μM amitriptyline, a level similar to that of chromaffin cell INa.

To assess the effect of the slowed recovery from inactivation in generating use-dependent blockade, DRG neurons were voltage-clamped and depolarized from −80 mV to 10 mV for 20 msec at a rate of 10 Hz. The results of a 10-Hz stimulus for 14 pulses is shown in figure 8, and the greater use-dependence in 10 μM amitriptyline is evident from the tracings of INa with subsequent depolarizations. The peak current of the nth depolarization (INa,n) could be described as an exponential function of the number of depolarizations following the initial peak current after rest (INa,1):

\[ I_{Na,n} = I_{Na,1}(1 - f(1 - \exp((1 - n)/b))] \]  

where \( f \) is percent of the peak INa that decreased with repetitive depolarization, and \( b \) is the rate constant of decline expressed as number of depolarizations. The solid lines in figure 8C are least-squares fits to equation 5 for the experimental traces in A and B. In the five cells studied in this manner, physiological use-dependence was evident in that control peak INa,1 decreased from 5.8 ± 1.2 to 5.1 ± 1.2 nA with the repetitive 10-Hz depolarizations, a 14 ± 6% decline. In 10 μM amitriptyline, mean INa,1 was 4.6 ± 1.4 nA and decreased to a steady-state of 3.4 ± 1.3 nA, a significantly greater decrease of 35 ± 7% (\( P = .012, \) paired t test). Rate constants \( b \) for control and in the presence of 10 μM amitriptyline, were 7.7 ± 1.3 and 7.6 ± 0.5 depolarizations, respectively. The resting block of INa,1 caused by amitriptyline was to 73 ± 8% of control, an effect identical to that observed in
chromaffin cells, but the steady-state depression by 10 μM amitriptyline at 10 Hz was to 56 ± 11% of the control steady-state INa at 10 Hz (P = .008, paired t test). Because fluoxetine did not show as marked a shift in steady-state inactivation, we examined its effect on use-dependent decline in INa by using a pulse protocol identical to that described in figure 8. In five experiments in DRG cells, the resting block of INa caused by 10 μM fluoxetine was to 51 ± 12% of control, while the steady-state use-dependent depression at 10 Hz was to 40 ± 13% of the control steady-state INa at 10 Hz (P = .031, paired t test). Despite a somewhat greater block of INa compared with amitriptyline, the use-dependent effect of fluoxetine appeared less prominent at 10 Hz.

To determine whether amitriptyline inhibition of neuronal Na⁺ channels would alter physiological processes, we examined AP behavior and INa in neonatal rat DRG neurons. Current-clamped neurons exhibited resting potentials ranging from −55 to −65 mV, consistent with previous work (Caviedes et al., 1990; Elliott and Elliott, 1993), and all-or-nothing APs in response to depolarizing current injections of +200 to +800 pA. In 4 of 7 neurons, sustained depolarizing current injection triggered bursts of 5.6 ± 0.8 Aps/stimulus of 200 msec in duration, as shown in figure 9A. The application of 20 μM amitriptyline reversibly decreased the number of APs evoked by the same depolarizing stimulus to 55 ± 4% of control. The inhibition followed the pattern illustrated in figure 9A, which is consistent with a use-dependent inhibition induced by amitriptyline. In the remaining neurons, that displayed only a single AP with current injection, a series of current steps were applied to assess changes in excitability. Although amitriptyline failed to alter the voltage response to a hyperpolarizing current injection of −30 mV (fig 9B), effects consistent with decreased membrane excitability were observed with depolarizing current pulses. Larger depolarizing current steps than those shown (typically >400 pA) did trigger APs, which were virtually indistinguishable between control and amitriptyline-treated conditions.

Discussion

In addition to the blockade of the cardiac Na⁺ channel, the TCAs inhibit the neuronal Na⁺ channel but with a far lower potency. The calculated neuronal Na⁺ channel Kᵦ value of ~20 μM for amitriptyline is similar to that for desipramine, 9 μM, previously reported in Myxicola giant axon (Schauf et al., 1975). Amitriptyline (10–30 μM) reduced AP amplitude and maximum rate of depolarization (dV/dtₘₐₓ) in crayfish giant axon (Wang et al., 1981), while TCAs inhibited 22Na⁺ influx in bovine chromaffin cells with IC₅₀ values of 10 to 17

Fig. 8. The use-dependent decline in current in peak INa under control conditions and after the application of 10 μM amitriptyline. P/4 subtraction was not used. A 20-msec depolarization from −80 to 10 mV was applied at a rate of 10 Hz in solution containing 30 mM Na⁺. A and B, Currents in response to the first, fourth, eighth and fourteenth depolarizations for control and with amitriptyline. C, Peak INa values from the experimental traces in A and B are plotted for 14 consecutive depolarizations. The curves fit to the peak currents are defined by the equation: INa,n = INa,1 (1 − f) exp(−(n−1)/b]], where INa,n is the peak INa of the first impulse (n = 1). For control and amitriptyline, the fractional use-dependent decline of current (f) was 2.2% and 44.7%, respectively, and the rate constant b was 7.4 and 8.9 depolarizations, respectively.

Fig. 9. Amitriptyline inhibits action potential activity in isolated rat neonatal DRG neurons. A, The DRG neuron was current-clamped and pulsed with a depolarizing current of +400 pA. In the presence of 20 μM amitriptyline (right), AP amplitude of the repetitively firing neuron was significantly attenuated. B, Another DRG neuron, which failed to show repetitive firing, was pulsed by current steps from −30, +70, +170 and +270 pA. The application of 20 μM amitriptyline decreased neuronal excitability with no apparent change in the hyperpolarizing response.
demonstrated a voltage-dependent reduction of INa from neuroblastoma cells by 3 μM imipramine, another TCA. In these neurally derived cells, the concentrations of amitriptyline and other TCAs required to cause >50% depression of INa is ~10 to 50 times higher than the 0.4 to 3.2 μM concentration of amitriptyline that is required for an equivalent effect in cardiac myocytes (Barber et al., 1991) and Purkinje fibers (Nattel, 1987) when stimulation rates are increased above 3 Hz.

Our results provide a more complete description of TCA action on steady-state inactivation and demonstrate the apparent stabilization by amitriptyline of an inactivated state that requires a more sustained repolarization to revert to an available closed state. Figure 6 predicts that after a repolarization for 80 to 100 msec, approximately twice as many channels will be inactivated in the presence of amitriptyline as in the control setting. Stabilization of the inactivated state by the antidepressants results in use-dependent blockade of Na+ channels, as evidenced in the DRG experiments with 10-Hz stimulation. Such rapid stimulation increased the depression of I Na by 10 μM amitriptyline from 27% for the initial depolarization to 44% for the steady-state 10 Hz I Na.

Based on competition experiments in myocytes, Barber et al. (1991) suggested that amitriptyline and lidocaine compete for the same LA binding site, recently shown to reside in the α-subunit (Ragsdale et al., 1994). It is noteworthy that the action of amitriptyline and the other TCAs is similar to the LAs in a number of regards. First, amitriptyline shifts the steady-state inactivation curve in the hyperpolarizing direction, just as the LAs. Second, amitriptyline depresses I Na in a frequency-dependent manner, while the degree of use-dependent inhibition may be somewhat less for the neuronal than the myocardial Na+ channels. Third, the cardiogenic Na+ channel is more sensitive than the neuronal type to blockade by amitriptyline. Likewise, the LA concentration required for equivalent inhibition in nerve is typically ~10-fold greater than that for myocardium if one compares studies of LA depression of I Na or action potential rate of depolarization (dV/dt) in myocardium vs. nerve. However, amitriptyline must have a 20- to 200-fold greater affinity for the LA binding site than do the LAs themselves if one compares the effective concentrations for Na+ channel or conduction blockade. It is noteworthy that TCAs have a tertiary amine group connected by a three carbon chain to a large aromatic moiety, while LAs have a tertiary amine connected to an aromatic group by a chain of two carbons and an amide (or ester) linkage.

The clinical relevance of such neuronal Na+ channel inhibition is unclear. There is considerable evidence demonstrating the analgesic effects of tricyclic (Hamneroff et al., 1984; Max et al., 1992; Valverde et al., 1994) and certain atypical (Max et al., 1992; Rani et al., 1996) antidepressants under differing clinical conditions of chronic pain. For example, the TCA doxepin has been shown to effectively treat migraine headache (Morland et al., 1979) and lower back pain (Hamneroff et al., 1982, 1984), and fluoxetine is a useful analgesic against rheumatic pain (Rani et al., 1996). Although the 1998 Antidepressant Block of Na+ Channels 213
References


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