A-Type K^+ Current in Neurons Cultured From Neonatal Rat Hypothalamus and Brain Stem: Modulation by Angiotensin II

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Wang, Desuo, Colin Sumners, Philip Posner, and Craig H. Gelband. A-type K^+ current in neurons cultured from neonatal rat hypothalamus and brain stem: modulation by angiotensin II. J. Neurophysiol. 78: 1021–1029, 1997. The regulation of A-type K^+ current (I_A) and the single channel underlying I_A in neonatal rat hypothalamus/brain stem cultured neurons were studied with the use of the patch-clamp technique. I_A had a threshold of activation between −30 and −25 mV (n = 14). Steady-state inactivation of I_A occurred between −80 and −70 mV and had a membrane voltage at which I_A was half-maximal at −52.2 mV (n = 14). The mean values for the activation and inactivation (decay) time constants during a voltage step to +20 mV were 2.1 ± 0.3 ms (n = 8) and 13.6 ± 1.9 ms (n = 8), respectively. Single-channel recordings from outside-out patches revealed A-type K^+ channels with voltage-dependent activation, 4-aminopyridine (4-AP) sensitivity, and inactivation kinetics similar to those of I_A. The single-channel conductance obtained from cell-attached patches was 15.8 ± 1.3 pS (n = 4) in a physiological K^+ gradient and 41.2 ± 3.7 pS (n = 5) in symmetrical 140 mM K^+. Angiotensin II (Ang II) (100 nM) markedly reduced single A-type K^+ channel activity by decreasing open probability (n = 4). The actions of Ang II on I_A and single A-type K^+ channels were reversible either by addition of the selective angiotensin type 1 (AT_1) receptor antagonist losartan (1 μM) or on washout of the peptide. Thus the activation of AT_1 receptors inhibits a tetraethylammonium-chloride-resistant, 4-AP-sensitive I_A and single A-type K^+ channels, and this may underlie some of the actions of Ang II on electrical activity of the brain.

INTRODUCTION

In the nervous system, A-type K^+ current (I_A) plays an important role in the control of excitability, synaptic input, and neurotransmitter release (Cull-Candy et al. 1989; Dye 1991; Mei et al. 1995; Sheng et al. 1993). I_A may be responsible for the initial repolarization of the action potential, contribute to afterhyperpolarization, promote pacemaker activity, and facilitate neuronal firing (Bouskila and Dudek 1995; Chandler et al. 1994; Connor and Stevens 1971; Dekin 1993; Ducreux and Puizillout 1995; Grolleau and Lapied 1995; MacDermott and Weight 1982). I_A has been studied in a variety of mammalian nervous tissues including sympathetic ganglia (Galvan and Sedlmeier 1984), hypothalamus and hippocampal brain slices (Bouskila and Dudek 1995; Greene et al. 1990; Zbicz and Weight 1985), neonatal supraoptic nucleus neurons (Cobbett et al. 1989), and embryonic hypothalamus neurons (Muller et al. 1992). Electrophysiologically, I_A can be identified by its unique voltage-dependent activation, fast kinetics of inactivation, and steady-state inactivation. Pharmacologically, I_A is aminopyridine sensitive and has been shown to be modulated by acetylcholine, glutamate, adenosine, and γ-aminobutyric acid (Akins et al. 1990; Hay and Lindsley 1995; Mei et al. 1995; Saint et al. 1990). The cloned K^+ channels from rat brain, RCK4 (Kv1.4) and Raw3 (Kv3.4), have been demonstrated to give rise to A-like currents (Pongs 1992; Schroter et al. 1991; Stuhmer et al. 1989).

Our previous work demonstrated that angiotensin II (Ang II), by activation of the angiotensin type 1 (AT_1) receptor subtype, caused a reversible and concentration-dependent decrease in delayed rectifier K^+ current (I_K) in rat cultured neurons from hypothalamus and brain stem (Kang et al. 1992; Sumners et al. 1996). Using a brain slice preparation, Nagamoto et al. (1995) reported that Ang II decreased the I_A amplitude by 21.3 ± 3.1% (mean ± SE) in supraoptic neurons, whereas Li and Ferguson (1996) demonstrated that by activation of AT_1 receptors, Ang II reduced I_A by 31.0 ± 4.1% in paraventricular nucleus cells.

The single K^+ channel that underlies I_A in cultured neurons has been characterized by several groups (Cooper and Shrier 1985; Kasai et al. 1986; Solc et al. 1987). Cooper and Shrier (1985) reported that in rat nodose sensory neurons A-type K^+ channel conductance was ~22 pS and ensemble averaged single-channel currents had similar inactivation kinetics to that of I_A. Kasai et al. (1986) observed a 20-pS A-type K^+ channel in guinea pig dorsal root ganglion cells. The conductance of single A-type K^+ channels in mammalian cultured neurons was greater than that of Drasophila neurons (5–8 pS) (Solc et al. 1987) and of cloned A-type K^+ channels (4.7–14 pS) (Stuhmer et al. 1989; Vega-Saenz de Miera et al. 1994). To date, Ang II regulation of the single channel underlying neuronal I_A has not been studied, although such modulation forms the basis for its action on whole cell currents and plays a role in modulating action potential firing patterns (see companion paper).

In this study, for the first time, we characterize a 4-aminopyridine (4-AP)-sensitive I_A and the single channel underlying it in rat cultured neurons with the use of the whole cell, outside-out, and cell-attached configurations of the patch-clamp technique. Furthermore, we demonstrate that the actions of Ang II on I_A and single A-type K^+ channel currents are mediated through the AT_1 receptor.

METHODS

Materials

One-day-old Sprague-Dawley rats were obtained from our breeding colony, which originated from Charles River Farms (Wilmington, MA). Losartan potassium was generously provided by
Electrophysiological recordings

Preparation of neuronal cultures

Neuronal cocultures were prepared from the brain stem and a hypothalamic block of 1-day-old Sprague-Dawley rats as described previously (Kang et al. 1992). Trypsin (375 U/ml) and DNase I (496 U/ml)-dissociated cells were resuspended in DMEM containing 1% PDHS and plated on poly-l-lysine-precoated 35-mm Nunc plastic tissue culture dishes. After cells were grown for 3 days at 37°C in a humidified incubator with 95% air-5% CO₂, they were exposed to 1 μM ARC for 2 days in fresh DMEM containing 10% PDHS. Then ARC was removed and the cells were incubated with DMEM (10% PDHS) for a further 9–12 days before use. At the time of use, cultures consisted of 90% neurons and 10% astrocyte glia, as determined by immunofluorescent staining with antibodies against neurofilament proteins and glial fibrillary acidic proteins (Sumners et al. 1990).

Electrophysiological recordings

Macroscopic and single-channel currents were recorded with the use of the whole cell, outside-out, and cell-attached patch-clamp configurations of the patch-clamp technique (Hamill et al. 1981). Experiments were performed at room temperature (22–23°C) with the use of an Axopatch-200A amplifier and Digidata 1200A interface (Axon Instruments, Burlingame, CA). Cells were bathed in Tyrode’s solution containing (in mM) 140 NaCl, 5.4 KCl, 2.0 CaCl₂, 2.0 MgCl₂, 0.3 NaH₂PO₄, 10 HEPES, and 10 dextrose, pH adjusted to 7.4 with NaOH. Neurons in the culture dish (volume 1.5 ml) were superfused at a rate of 2–4 ml/min. The patch electrodes (Kimax-5.1, Kimber Glass, Toledo, OH) had resistances of 3–4 MΩ when filled with an internal pipette solution containing (in mM) 140 KCl, 2 MgCl₂, 5 ethylene glycol-bis-(β-aminoethyl ether)-N,N,N',N''-tetraacetic acid (EGTA), 4 ATP, 0.1 guanosine 5'-triphosphate, 10 dextrose, and 10 HEPES, pH adjusted to 7.2 with KOH. Cell-attached patches were formed by sealing the patch electrode to the cell body. Single-channel activity was recorded from patches with a seal resistance >5 GΩ. The whole cell configuration was formed by applying negative pressure to the patch electrode. For whole cell recordings, cell capacitance was canceled electronically and the series resistance (<10 MΩ) was compensated by 75–80%. Outside-out patches were formed by slowly elevating the patch electrode away from the cell body after formation of the whole cell configuration. A junction potential of ~10 mV was corrected for all command potentials.

Sodium current (I₅Na) was blocked by TTX (100 nM). Calcium current (I₅Ca) was blocked by CdCl₂ (100 μM). Ca²⁺-activated K⁺ current (I₅KCa) was reduced to insignificant levels by omitting CaCl₂ from the pipette solution, blocking I₅Na with CsCl, and buffering intracellular free Ca²⁺ with EGTA. In most of the experiments, I₅KCa was blocked by extracellular TEA (140 mM), which replaced the NaCl (140 mM).

To evaluate the steady-state inactivation of I₅, a depolarizing test pulse to +42.5 mV (200 ms in duration) was preceded by conditioning pre pulses from −102.5 to −5 mV in 7.5-mV steps (1 s in duration). I₅ was measured as the peak current amplitude elicited by the depolarizing test pulses and expressed as the membrane conductance [g₅ = I₅/(V₅ – Vₑ)], where V₅ is membrane potential and Vₑ is the K⁺ equilibrium potential (~82 mV) determined from the concentration gradient with the assumption that intracellular K⁺ was equal to pipette potassium (140 mM). In some cases, I₅ was converted to conductance values (nS).

In outside-out patch-clamp experiments, single A-type K⁺ channel activity was elicited with the use of pulses from ~100 mV to various test potentials (0 to +40 mV). In cell-attached patch-clamp experiments, A-type K⁺ channel activity was elicited either with the use of voltage steps from +40 mV to various test potentials (~100 to 0 mV) when patch pipettes were filled with Tyrode’s solution (5.4 mM KCl) or by pulses from ~100 mV to various test potentials (~20 to +100 mV) when patch pipettes were filled with 140 mM KCl. For convenience, the current-voltage relationship for single-channel currents obtained from cell-attached patches was constructed by plotting single-channel current amplitude as a function of voltage (the pipette potential minus the average resting potential), ~60 mV when the bath contained normal Tyrode’s solution and ~20 mV when the bath contained 140 mM TEA.

Data acquisition and analysis were performed with the use of pCLAMP 6.03. Whole cell currents were filtered at 1 kHz (frequency filter ~3 dB) and digitized at 2 kHz. Single-channel currents were filtered at 2 kHz (frequency filter ~3 dB) and digitized at 10 kHz. By convention, outward current is depicted as upward deflections of current.

Data analysis

Results are expressed as means ± SE. Statistical significance was evaluated with the use of paired t-test. Differences were considered significant at P < 0.05; n corresponds to the number of cells examined. Open probability (OP) for single A-type K⁺ channels was obtained during 100-ms depolarizing pulses.

RESULTS

Neurons used for the experiments had an oval- or triangular-shaped cell body with two or three small and short processes that did not form a network with adjacent cells. The maximum diameter of the neurons was ~15–25 μm. The passive membrane input resistance of the cells was 301.4 ± 21.7 MΩ (n = 45). The average cell capacitance was 51.15 ± 2.1 pF (n = 73). Typical neuronal action potentials, either spontaneous or stimulated, were present in these cells (see companion paper). There were at least four transmembrane currents that underlie the depolarization and repolarization of the action potential. These are defined as 1) TTX-sensitive I₅Na, 2) Cd²⁺-sensitive I₅Ca, 3) TEA-sensitive I₅K, and 4) 4-AP-sensitive transient K⁺ current (I₅). The present work focuses on the 4-AP-sensitive I₅.

Isolation of I₅

In normal Tyrode’s solution, when I₅Na and I₅Ca were blocked by TTX (100 nM) and Cd²⁺ (100 μM), respectively, a voltage-dependent total outward current was recorded (Fig. 1A). The total outward current could be pharmacologically dissected into at least two components. When TEA (140 mM) was bath applied, significant inhibition of a delayed-rectifier-like K⁺ current was observed (Fig. 1B). Subtracting the current traces in Fig. 1B from those in Fig. 1A reveals an outward K⁺ current that is defined as a volt-
Isolation of neuronal A-type K⁺ current (I_A). Sodium current (I_Na) and calcium current (I_Ca) were blocked by tetrodotoxin (TTX, 100 nM) and Cd²⁺ (100 μM), respectively. Cell membrane potential was held at −90 mV. A: total outward current traces elicited by 200-ms depolarizing pulse from −35 to +42.5 mV in 7.5-mV steps following 1-s prehyperpolarizing pulse to −110 mV. B: current traces recorded in presence of external tetraethylammonium chloride (TEA, 140 mM). C: TEA-sensitive difference current [A − B], mainly delayed rectifier K⁺ current (I_K). D: current traces recorded in presence of TEA and 4-aminopyridine (4-AP, 5 mM). E: TEA-resistant, 4-AP-sensitive transient difference current (I_A) obtained by subtracting currents recorded in presence of 4-AP from currents recorded in absence of 4-AP (i.e., B − D). F: conductance-voltage relationship (current amplitude was measured as peak current during depolarizing pulse) of I_A. These results are representative of 14 cells.

Biophysical properties of I_A

Steady-state inactivation of I_A was studied in a total of 14 neurons. The steady-state inactivation current traces of I_A were obtained with the use of the voltage paradigms described in the METHODS section. The peak amplitude of I_A elicited by repetitive depolarizing pulses (+42.5 mV) began to decrease at conditioning potentials of −80 to −70 mV (Fig. 3, A and C). When the conditioning potential was more positive than −65 mV, steady-state inactivation became accelerated and complete inactivation occurred at a conditioning potential of −27.5 mV. The averaged steady-state inactivation data were fit with the following Boltzmann function

\[
g_A / g_{A\text{max}} = \left\{ 1 + \exp \left[ \left( V - V_{1/2} \right)/k \right] \right\}^{-1}
\]

where \(g_A / g_{A\text{max}}\) is the conductance normalized to its maximum value, \(V\) is the membrane potential, \(V_{1/2}\) is the mem-
brane voltage at which $I_A$ is half-maximum, and $k$ is the Boltzmann slope factor. The averaged data, when fit with a Boltzmann function, revealed a half-steady-state inactivation potential ($V_{1/2}$) of $-52.2$ mV and a voltage-sensitive slope factor ($k$) of $-6.5$ mV.

The activation and inactivation (decay during a voltage step) time constants of the 4-AP-sensitive $I_A$ were studied in eight neurons. Figure 3A shows a representative trace of $I_A$ during a 200-ms depolarizing voltage step from $-110$ to $+42.5$ mV. The activation (rising) and the inactivation (decaying) phases of the current were fit best by a single-exponential equation

$$I = I_{\text{max}}[1 - \exp(-t/\tau)]$$

where $I$ is the amplitude of $I_A$ at time $t$, $I_{\text{max}}$ is the peak $I_A$ at time 0, and $\tau$ is the time constant for activation or inactivation. In this experiment, activation and decay time constants were 1.4 and 14.3 ms, respectively. The mean values of activation and inactivation time constants for a depolarizing pulse to $+20$ mV were $2.1 \pm 0.3$ ms and $13.6 \pm 1.9$ ms, respectively.

![FIG. 3. Activation and inactivation time constants of $I_A$. A: representative $I_A$ trace (---) elicited by depolarizing pulse from $-110$ to $+42.5$ mV. Dashed lines are obtained by fitting rising (activation) and decay phases (inactivation) of current trace with 1st-order exponential equation. B: mean data showing voltage dependence for activation time constant ($n = 8$). C: mean data showing voltage dependence for inactivation time constant ($n = 8$).](image)

The time to reach peak activation of $I_A$ was voltage dependent (Fig. 3B). The greater the depolarization, the faster $I_A$ activated. For example, $\tau$ was equal to $4.0 \pm 0.6$ ms during a depolarizing pulse to $+5$ mV but was only $1.1 \pm 0.1$ ms during a voltage step to $+42.5$ mV. In comparison, the inactivation (decay) time constant of $I_A$ was voltage dependent only when the depolarizing potential was more negative than 0 mV. When the depolarizing test potential was more positive than 0 mV, the decay time constant showed little voltage dependence (Fig. 3C).

**Single-channel characteristics of 4-AP-sensitive $I_A$**

Single neuronal A-type K$^+$ channel currents were recorded from both cell-attached and outside-out patches. In a physiological external K$^+$ solution [K$^+$ concentration in the pipette ([K$^+$]$_{\text{pip}}$) = extracellular K$^+$ concentration ([K$^+$]$_{\text{o}}$) = 5.4 mM], A-type K$^+$ channel activity occurred...
Angiotensin II regulation of neuronal A current

Ang II regulation of $I_A$

We next examined the pharmacological regulation of $I_A$ by Ang II in the presence of the AT$_2$ receptor antagonist PD 123319 (1 μM). PD 123319 had no effect on baseline $K^+$ current or channel activity. Ang II, when superfused into the recording chamber, significantly reduced $I_A$ in a dose-dependent manner (Fig. 6, A and B, asterisk: $P < 0.01, n = 12$ for Ang II (100 nM), $n = 5$ for the other concentrations). Therefore we chose to use a maximum effective dose of Ang II, 100 nM, in the rest of our experiments. Ang II (100 nM) reduced peak $I_A$ and shifted the activation curve to the right in eight neurons tested (Fig. 7). Figure 7A shows a...
representative experiment in which Ang II decreased the peak amplitude of $I_A$ elicited by depolarizing test pulses from a holding potential of $-110$ mV to $+20$ mV. The effect of Ang II was reversed by addition of the selective AT$_1$ receptor antagonist losartan ($1 \mu$M) to the superfusate solution. The mean data for the Ang II-mediated decrease in $I_A$ are illustrated in Fig. 7, B and C. Ang II caused a decrease of $\sim 20\%$ in $I_A$ at $+20$ mV (Fig. 7B). Ang II also shifted the $I_A$ conductance-voltage relationship $\sim 8\%$ to right (Fig. 7C).

Cell-attached patches were used to evaluate the ability of Ang II to modulate the activity of A-type K$^+$ channels. Figure 8 shows representative single-channel current traces and ensemble averaged currents of A-type K$^+$ channels recorded in the absence and presence of Ang II (100 nM). Single-channel activity was elicited by a voltage step of $+100$ mV ($V_{pop} - V_M = 100$ mV). There were two A-type K$^+$ channels in this patch that activated at the beginning of the step and inactivated after $\sim 40$ ms (Fig. 8, left). Ang II markedly reduced the activity of A-type K$^+$ channels without affecting the single-channel current amplitude (Fig. 8, middle). Similar to the effects on $I_A$, the actions of Ang II were reversed either on washout (Fig. 8, right) or by addition of losartan ($1 \mu$M) to the superfusate solution (data not shown). The ensemble averaged current is illustrated below the single-channel current traces and reflects control, application of Ang II, and washout, respectively. The ensemble averaged data are markedly similar to those data for Ang II regulation of $I_A$ illustrated in Fig. 7. Similar results were observed in four other cell-attached patches. Figure 9 illustrates the effects of Ang II on single-channel $NP_o$. The data in Fig. 9 were used to generate amplitude histograms and calculate $NP_o$. Under control conditions, in the presence of Ang II (100 nM), and after washout, $NP_o$ was 0.21, 0.10, and 0.16, respectively. The mean values for $NP_o$ under these conditions were $0.22 \pm 0.04, 0.10 \pm 0.08$, and $0.17 \pm 0.11$, respectively ($n = 4$).

**DISCUSSION**

The transient outward K$^+$ current reported here was defined as a TEA-resistant, 4-AP-sensitive A current ($I_A$). This conclusion was based on the following criteria. First, under our experimental conditions, $I_{Na}$, $I_C$, $I_K$, and $I_{K,Ca}$ were blocked by TTX, Cd$^{2+}$, TEA, and internal EGTA, (5 mM) respectively. Second, the voltage dependence and the kinetics of activation and inactivation of $I_A$ were similar to previously published results (Figs. 1–3) (Bouskila and Dudek 1995; Mei et al. 1995). Finally, the single-channel conductance demonstrated for channels that underlie $I_A$ was similar to that reported for other neuronal preparations (Figs. 4 and 5) (Cooper and Shrier 1985; Kasai et al. 1986).

This study also demonstrated that Ang II, via activation of AT$_1$ receptors, reduced $I_A$ and decreased the activity of a 15-pS, rapidly inactivating, 4-AP-sensitive K$^+$ channel (Figs. 8 and 9). Our previous studies showed that hypothalamic neurons contained $\sim 70\%$ AT$_2$ and $\sim 30\%$ AT$_1$ receptors (Sumners and Raizada 1993; Sumners et al. 1991, 1994). We previously determined that activation of AT$_1$ receptors by Ang II decreases net outward current via inhibiting $I_C$ and stimulating $I_{K,Ca}$, which was dependent on protein kinase C activation (Sumners et al. 1996). Our recent study also showed that intracellular injection of a 25-amino-acid peptide corresponding to the third intracellular loop of the cloned AT$_1a$ receptor (AT$_{1a,c13}$) elicited changes in $I_K$ and $I_{Ca}$ that were similar to those obtained with application of Ang II via AT$_1$ receptors. By contrast, injection of a 19-amino-acid peptide corresponding to the second intracellular loop did not modulate $I_K$ or $I_{Ca}$. Importantly, our data elucidated that the modulation of neuronal $I_K$ and $I_{Ca}$ by AT$_{1a,c13}$ involves protein kinase C, inositol-(1,4,5)-trisphosphate (IP$_3$), and intracellular Ca$^{2+}$, similar to the AT$_1$ receptor modulation of $I_K$ and $I_{Ca}$ by Ang II (Zhu et al. 1997). These effects are consistent with the increases in neuronal activity observed following AT$_1$ receptor activation (Ambuhl et al. 1992; Yang et al. 1992). Combined with our present findings, we suggest that by potentiating $I_C$, and diminishing $I_K$ and $I_A$, Ang II increases the excitability of neurons from the hypothalamus and brain stem. This too is consistent with our recent observation that Ang II increases the spontaneous firing rate of the cultured neurons (see companion paper).

Ang II produced three important biophysical, physiologi-
FIG. 8. Effects of Ang II on single $I_A$ recorded from cell-attached patches. Experiments were performed under same conditions as Fig. 4. Currents were activated by driving force of +100 mV ($V_{m} = $ membrane potential = +100 mV). Left: control single-channel currents and ensemble average current. Middle: effects of bath application of Ang II (100 nM) on single-channel activity and ensemble average current. Right: recovery on washout of Ang II. This is representative of 4 experiments.

Biophysically and pharmacologically, we have also characterized $I_A$ and single A-type K$^+$ channels from these neurons. $I_A$ and single A-type K$^+$ channels showed voltage-dependent activation and steady-state inactivation parameters similar to those reported previously (Bouskila and Dudok 1995; Cooper and Shrier 1985; Kasai et al. 1986; Mei et al. 1995). However, $I_A$ and single A-type K$^+$ channels recorded in this study displayed different inactivation kinetics when compared with the results of Cooper and Shrier (1985) and Kasai et al. (1986). Our present results show that $I_A$ and single A-type K$^+$ channels had time constants of inactivation of 14 ms (Fig. 3) and 15 ms (Fig. 5), respectively. Data from Cooper and Shrier (1985) and Kasai et al. (1986) show that $I_A$ and single A-type K$^+$ channels had inactivation time constants of 30 and 100 ms, respectively.
The similarity in steady-state inactivation and differences in inactivation kinetics during a voltage step in different neuronal preparations may be due to specific molecular mechanisms involving the coexistence of N-type and C-type inactivation mechanisms in A-type K⁺ channels (Armstrong and Bezanilla 1977; Baukrowitz and Yellen 1995; Choi et al. 1991; Griswold and Cahalan 1989; Yellen et al. 1994; Zagotta et al. 1990).

The conductance of single A-type K⁺ channels recorded under the cell-attached configuration is related to the transmembrane potassium gradient. It is well accepted that the A-type K⁺ channels have a small conductance (∼15–20 pS, Fig. 4) (Rudy 1988) in a physiological K⁺ gradient ([K⁺]o = 5.4 mM). Finally, pharmacologically I[K]
A and single A-type K⁺ channels from neurons of the hypothalamus and brain stem resemble other neurons in their 4-AP sensitivity. Kasai et al. (1986) reported that 4-AP blocked A-type K⁺ channels from the inside of the cell by diffusing through the membrane. We also observed that bath application of 4-AP could inhibit I[K]
A (Fig. 1) and single A-type K⁺ channel activity recorded in outside-out patches (Fig. 5).

In summary, we have characterized a TEA-resistant, 4-AP-sensitive I[K]
A and the single channel underlying it in rat cultured neurons with the use of whole cell, outside-out patch, and cell-attached patch configurations. We have also shown that Ang II, through activation of AT₁ receptors, inhibits I[K]
A and single A-type K⁺ channels. The Ang II regulation of neuronal I[K]
A is one of the bases for its physiological actions through changes in action potential firing patterns in the brain. Future experiments will include the elucidation of the signal transduction mechanism(s) involved in Ang II regulation of I[K]
A.

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