Inhibition of Astroglial Inwardly Rectifying Kir4.1 Channels by a Tricyclic Antidepressant, Nortriptyline

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Received August 7, 2006; accepted October 26, 2006

ABSTRACT

The inwardly rectifying K⁺ (Kir) channel Kir4.1 is responsible for astroglial K⁺ buffering. We examined the effects of nortriptyline, a tricyclic antidepressant (TCA), on Kir4.1 channel currents heterologously expressed in HEK293T cells, using a whole-cell patch-clamp technique. Nortriptyline (3–300 μM) reversibly inhibited Kir4.1 currents in a concentration-dependent manner, whereas it marginally affected neuronal Kir2.1 currents. The inhibition of Kir4.1 channels by nortriptyline depended on the voltage difference from the K⁺ equilibrium potential (Eₖ), with greater potency at more positive potentials. Blocking kinetics of the drug could be described by first-order kinetics, where dissociation of the drug slowed down and association accelerated as the membrane was depolarized. The dissociation constant (Kₛ) of nortriptyline for Kir4.1 inhibition was 28.1 μM at Eₖ. Other TCAs, such as amitriptyline, desipramine, and imipramine, also inhibited Kir4.1 currents in a similar voltage-dependent fashion. This study shows for the first time that nortriptyline and related TCAs cause a concentration-, voltage-, and time-dependent inhibition of astroglial K⁺-buffering Kir4.1 channels, which might be involved in therapeutic and/or adverse actions of the drugs.

Astrocytes are the major cell component of brain glia and contribute to a number of cerebral functions. They form the blood-brain barrier by surrounding capillaries, maintain water and extracellular ion homeostasis, metabolize neurotransmitters, and supply nutrients to neurons (Kofuji and Newman, 2004; Simard and Nedergaard, 2004). Among these functions, “spatial potassium buffering” by astrocytes is critical in maintaining neuronal excitability. This removes excess extracellular potassium ions (K⁺) from the sites of high neuronal activity and transports them unidirectionally to the regions of low K⁺, such as blood vessels (Walz, 2000; Higashi et al., 2001; Kofuji and Newman, 2004; Simard and Nedergaard, 2004). In the resting state, neurons are bathed in extracellular fluid that contains approximately 3 mM K⁺. Neuronal excitation causes considerable release of K⁺ from the neuronal membrane, especially at synaptic sites, which easily results in elevation of the extracellular K⁺ concentration ([K⁺]ₑ) to approximately 10 mM (Walz, 2000; Kofuji and Newman, 2004). If uncorrected, this would cause sustained depolarization of neural membranes and, finally, cessation of synaptic transmission.

The spatial buffering of K⁺ is considered to be mediated at least partly by Kir channels expressed in astrocytes (Kofuji and Newman, 2004; Simard and Nedergaard, 2004). The Kir channel family comprises more than 15 members that fall into seven subfamilies (Kir1.x through Kir7.x) (Kubo et al., 2005). It was shown that, among them, Kir4.1 and Kir5.1 are expressed predominantly in brain astrocytes and Müller cells (Tanemoto et al., 2000; Higashi et al., 2001). Thus, depending on the difference between local Eₖ and the membrane potential of astrocytes, these Kir channels can mediate either absorption or extrusion of K⁺ across the astroglial cell membrane and thus can act as the spatial K⁺-buffering current. In addition, Kir4.1 channel and the water channel, aquaporin-4, are colocalized in certain membrane domains of brain astrocytes and Müller cells, suggesting that spatial K⁺

ABBREVIATIONS: Kir, inward rectifying K⁺; TCA, tricyclic antidepressant; GFP, green fluorescent protein.
buffering may couple with water movement across the astroglial membrane (Nagelhus et al., 1999; Amiry-Moghadam et al., 2003; Puwarawuttipanit et al., 2006). Therefore, Kir channels containing Kir4.1 may be involved in various physiological and pathological processes in the brain. However, few studies have been performed on the functional control of Kir4.1 channels so far, with the exception of the effects of intracellular acidification (Tanemoto et al., 2000; Pessia et al., 2001; Casamassima et al., 2003).

Because the astrocyte is one of the target sites for antidepressants (Malberg and Blenky, 2005) and various potassium channel blockers are known to induce antidepressant actions in animals (Guo et al., 1995, 1996; Kaster et al., 2005), we conducted a patch-clamp study to evaluate the actions of tricyclic antidepressants (TCAs) on the astroglial Kir4.1 channels expressed in HEK293T cells. The present study demonstrated for the first time that nortriptyline and other TCAs, including amitriptyline, desipramine, and imipramine, inhibited homomeric Kir4.1 channels in a voltage- and time-dependent fashion. This might be involved in the therapeutic and/or adverse actions of the drugs.

Materials and Methods
Transfection and Cell Culture. Human Kir4.1 inserted into an IRES vector (pIRES-DeR2; Clontech, Mountain View, CA) was a kind gift from Dr. S. Hirose (Fukuoka University, Fukuoka, Japan). We transiently expressed this construct in HEK293T cells using FuGENE6 transfectant (Roche Diagnostics, Tokyo, Japan). A secondary GFP marker plasmid (pCA-GFP) was cotransfected in a DNA mass ratio favoring the Kir4.1 construct 5-fold (i.e., 0.05 versus 0.25 μg) (Chemin et al., 2001). Control and transfected cells were kept in Dulbecco’s modified Eagle’s medium (Sigma-Aldrich, St. Louis, MO) supplemented with 10% (v/v) fetal bovine serum (Sigma-Aldrich) and 1% (v/v) antibiotic/antimycotic cocktail (Invitrogen, Carlsbad, CA), containing penicillin, streptomycin, and amphotericin B. The cells were kept in a humidified 5% CO2/37°C environment with a 3-day passing cycle. Before the experiments, the cells were dissociated with 0.05% trypsin/EDTA (Invitrogen) and seeded onto poly-L-lysine-coated (Sigma-Aldrich) glass coverslips. In some experiments, the HEK cells were transfected with mouse Kir2.1 inserted into pCDNA3 (Invitrogen) as described above.

Solutions and Drugs. The bathing solution used for electrophysiological experiments contained 112 mM NaCl, 30 mM KCl, 5 mM HEPES, 2 mM CaCl2, 0.53 mM MgCl2, and 5.5 mM glucose, pH 7.4. To determine the influence of [K+]o on the nortriptyline blockade of Kir 4.1 channels, we substituted K+ with Na+ in the bath solution to obtain a final [K+]o of 10, 30, or 100 mM. Recording pipettes were filled with an internal solution containing 140 mM KCl, 2 mM MgCl2, 5 mM EGTA, and 5 mM HEPES (adjusted to pH 7.25 with KOH).

Nortriptyline hydrochloride, imipramine hydrochloride, amitriptyline hydrochloride, and desipramine hydrochloride were purchased from Sigma-Aldrich. Stock solutions (nortriptyline, 30 mM; all others, 100 mM) were prepared with distilled water and stored at 4°C until the day of the experiment. All other reagents were obtained from commercial sources.

Electrophysiology and Data Analyses. Twenty-four to 72 h after transfection, a coverslip carrying transfected cells was transferred to the stage of an inverted fluorescence microscope (Axiovert 135; Carl Zeiss, Tokyo, Japan) and continuously superfused with a gravity-driven perfusion system. Experiments were conducted at room temperature. The electrodes filled with the internal solution had a resistance of 1.2 to 1.5 MΩ. The transfected cells were identified by GFP expression and used for the whole-cell clamp experiments. The currents were measured with an Axopatch 200A amplifier (Axon Instruments, Union City, CA). The clamping voltage and the associated macroscopic currents were monitored on a dual beam oscilloscope, fed through a VR-10B PCM digital data recorder (InstruTECH Corporation, Port Washington, NY), and stored on video tape. For analysis, the data were reproduced off-line, digitized, and low-pass-filtered at 1.0 kHz (~3 dB) with an eight-pole Bessel filter (NF Electronic Instruments, Yokohama, Japan). These data were analyzed with Pulse Program (Heka Electronic, Lambrecht, Germany) and Patch Analyst Pro version 1.23 (MT Corporation, Hyogo, Japan). The data fitting, unless otherwise described in the text, involved least-squares linear regression analysis. All data points represent the mean ± S.E.M.

Results
Effects of Nortriptyline on Kir4.1 and Kir2.1 Channel Currents. Nortriptyline was applied to a HEK293T cell transfected with Kir4.1 cDNA (Fig. 1A). The cell was held at −40 mV (~E Kahn = 30 mM). Voltage step pulses (300 ms in duration) were successively applied to −110 and +30 mV with a 200-ms interval between them. This set of voltage steps was repeated every 5 s. In control conditions, a large inward K+ current was evoked during hyperpolarizing steps, whereas a small but significant outward K+ current was seen during depolarizing steps, illustrating the intermediate inwardly rectifying character of expressed Kir4.1 channels. When nortriptyline (100 μM) was added to the bath, both outward and inward currents were markedly inhibited. The nortriptyline-induced inhibition of Kir4.1 current was reversible and returned to the control level after washout of the drug. During a hyperpolarizing pulse, although the Kir4.1 current showed slight reduction after an instantaneous current jump in the control, in the presence of nortriptyline, the initial jump was greatly reduced, and the current then gradually increased. When Ba2+ (3 mM) was added to the bath at the end of the experiment, it inhibited the current completely.

In Fig. 1B, the drug was applied to a cell expressing Kir2.1 channels. The expressed current exhibited strong inward rectification with a large inward current at −110 mV but practically no outward current at +30 mV. Nortriptyline (100 μM) only slightly reduced the inward current, whereas Ba2+ (3 mM) completely suppressed it.

Figure 1C shows a current-voltage relationship of Kir4.1 currents recorded from the same HEK293T cell in response to various concentrations of nortriptyline. The cell was held at −35 mV in 40 mM [K+]o, and given with a 500-ms step pulse from −160 to +60 mV (by 20 mV) every 2 s. The magnitude of inhibition was less prominent at hyperpolarized potentials than at depolarized potentials. High concentrations of nortriptyline virtually abolished Kir4.1 currents at depolarizing potentials, whereas they still permitted some inward K+ currents at hyperpolarizing potentials. The blockade of Kir4.1 by nortriptyline therefore seems to be voltage-dependent.

Figure 1D shows the concentration-dependent effects of nortriptyline on Kir4.1 channel at +30 and −110 mV (Fig. 1A) and on Kir2.1 at −110 mV (Fig. 1B). The relationships were fitted with the following Hill’s equation:

\[ f(D) = \frac{1}{1 + (D/IC_{50})^n} \]
Transiently transfected HEK293T cells were voltage-clamped at a holding potential of 0 mV, and the cells were superfused with bathing solutions containing 10, 30, or 100 mM [K+]o. The cells were clamped at the voltage corresponding to EK in each [K+]o, and command voltage steps (15 s in duration) to various potentials were applied every 60 s. Figure 2A shows typical current traces before and after application of 100 μM nortriptyline in 30 or 100 mM [K+]o. In both cases, the drug almost completely abolished outward currents elicited by

Since above studies revealed that the nortriptyline dissociates from Kir4.1 channels during hyperpolarized step pulse, step pulses with longer duration seemed to be required to allow a steady-state reaction. Therefore, we employed long-duration (i.e., 15-s) step pulses in the following experiments to evaluate the steady-state kinetics of the nortriptyline inhibition.

**Effects of Extracellular K⁺ Concentration on the Voltage Dependence of Nortriptyline-Induced Blockade of Kir4.1 Channels.** We analyzed the effects of extracellular K⁺ concentration ([K+]o) on nortriptyline blockade of Kir4.1 channels (Fig. 2). The cells were superfused with bathing solutions containing 10, 30, or 100 mM [K+]o. They were clamped at the voltage corresponding to EK in each [K+]o, and command voltage steps (15 s in duration) to various potentials were applied every 60 s. Figure 2A shows typical current traces before and after application of 100 μM nortriptyline in 30 or 100 mM [K+]o. In both cases, the drug almost completely abolished outward currents elicited by
voltage steps positive to $E_K$. On the other hand, the inhibited Kir 4.1 currents by nortriptyline gradually increased at potentials negative to $E_K$, indicating that dissociation of nortriptyline was occurring during the 15-s voltage step. The time course of the action of the drug during each voltage step was obtained by dividing the current recorded in the presence of the drug with the control. The current ratio ($I_{\text{Drug}}/I_{\text{Control}}$) during each voltage step could be well fitted with a single exponential function (Fig. 2A, bottom traces),

$$f(t) = -Ae^{-\tau t} + P_o$$

where $t$ is the time, $\tau$ is the time constant, $P_o$ is the open probability that represents the fraction of unblocked channels at steady state, and $A$ is the difference between the initial current ratio at the onset of pulse and $P_o$. This indicates that the kinetics of drug-action largely follow a first-order reaction between unblocked and blocked states independent of the control gating of Kir4.1 channels. Therefore,
we could obtain values for $P_o$ and $\tau$ for the action of the drug from these data.

Figure 2, B and C, shows $P_o$ and $\tau$ at each potential with 10, 30, and 100 mM $[K^+]_o$. Both $P_o$ and $\tau$ were voltage-dependent. With increasing $[K^+]_o$, the curves for $P_o$ and $\tau$ were shifted in parallel to the right. The voltage dependence of $P_o$ was analyzed with the following Boltzmann function:

$$f(V) = \frac{A_1 - A_2}{1 + e^{(V - V_{1/2})/k}} + A_2$$

(3)

where $f(V)$ is $P_o$ at a given potential ($V$), $V_{1/2}$ is the voltage where 50% of the channels are blocked, $k$ is the slope factor of the fit, and $A_1$ and $A_2$ are the maximal and minimal $P_o$, respectively. The fits of the $P_o$ curves yielded $V_{1/2}$ values of $-124 \pm 0.4$ ($k = 11.3 \pm 0.9$), $-93 \pm 0.8$ ($k = 9.8 \pm 0.6$), and $-67 \pm 1.9$ ($k = 12.1 \pm 1.7$) mV for 10, 30, and 100 mM $[K^+]_o$, respectively. The corresponding $V_{1/2}$ shifts were 31 and 26 mV, which correlated well with the shifts in $E_K$ between 10 and 100 mM $[K^+]_o$, respectively. Although fitting of Boltzmann functions to the data for $\tau$ was not possible because the data at potentials positive to $E_K$ were lacking in this set of experiments, the data also shifted to the right with increasing $[K^+]_o$ in a fashion similar to that of $P_o$ (Fig. 2C). Therefore, it is strongly suggested that the blocking kinetics of Kir4.1 by nortriptyline depend on the voltage difference from $E_K$.

**Kinetics of Nortriptyline-Induced Blockade of Kir4.1 Channels.** We next examined the effects of drug concentration on the inhibition of Kir4.1 channels at 30 mM $[K^+]_o$. The cells were held at $-40$ mV ($=E_K$ for 30 mM $[K^+]_o$), and voltage steps to various potentials were applied in the presence of different concentrations of nortriptyline (10, 30, or 100 $\mu$M). The current ratios ($I_{Drug}/I_{Control}$) obtained at each concentration of nortriptyline could be well fitted with single exponential functions (Fig. 3A). From the fits, the steady-state $P_o$ and $\tau$ for the nortriptyline inhibition were estimated at each concentration of the drug (Fig. 3, B and D). Because the $\tau$ values at the potentials positive to $E_K$ were difficult to measure because of the small amplitude of outward Kir4.1 currents, they were estimated with the double-pulse protocol as shown in Fig. 3C. The cells were first stepped to a longer hyperpolarizing potential at $-110$ mV ($P_1$, 15-s duration) from the holding potential at $-40$ mV ($=E_K$ for 30 mM $[K^+]_o$) to allow for complete dissociation of nortriptyline. The cells were then clamped at different membrane potentials between $E_K$ ($-40$ mV in this trace) and $E_{K\pm 50}$ for various intervals ranging from 0.1 to 16.3 s. Then, the second step pulse to $-110$ mV ($P_2$, 200-ms duration) were applied. The resulting traces were superimposed and fitted with a single exponential function to estimate $\tau$ at the depolarized potentials (Fig. 3C). As the concentration of nortriptyline was increased from 10 to 30 and 100 $\mu$M, $P_o$ and $\tau$ values decreased (Fig. 3, B and D).

Because the blocking kinetics of nortriptyline could be fitted with a single exponential curve, it was suggested that its mechanism can be largely described with a first-order reaction model independent of control channel gating, as shown below:

$$\beta^a$$

$U \xrightarrow{\alpha} B$  

(4)  

where $U$ and $B$ represent unblocked and blocked state of the channel with nortriptyline, respectively. $\beta^a$ represents the apparent association rate constant, and $\alpha$ is the dissociation rate constant. $\alpha$ and $\beta^a$ were calculated from $P_o$ and $\tau$ at each potential (Fig. 3, B and D) according to the following equations, with the exception of the points where the Kir4.1 inhibition was saturated ($P_o = 0$ with 100 $\mu$M nortriptyline at $E_{K-20}$ to $E_{K+50}$):

$$\alpha = P/\tau$$

(5)

$$\beta^a = (1 - P_o)/\tau$$

(6)

The $\alpha$ for nortriptyline inhibition decreased as the membrane potential was depolarized, regardless of the drug concentration (Fig. 4A). When fitted with the Boltzmann equation, $\alpha$ had a half-maximal value at $-100.5$ mV ($V_{1/2}$), with a slope factor of 7.8, and became constant at $\sim 0.05$ s$^{-1}$ ($A_2$) at potentials above $E_K$. The $\beta^a$, on the other hand, was concentration-dependent and increased with depolarization (Fig. 4B). The association rate constant ($\beta$) after normalizing $\beta^a$ with the drug concentration ($\beta = \beta^a/[\text{Nortriptyline}]$) was still voltage-dependent and increased with depolarization (Fig. 4C). The $K_d$ value of nortriptyline ($K_d = \alpha/\beta$) was estimated as 28.1 $\mu$M at $E_K$.

**Effect of Other TCAs on Kir4.1 Currents.** We next examined whether the inhibition of Kir4.1 channel currents is common to TCAs or specific to nortriptyline (Fig. 5). The protocols used were the same as Fig. 1A. All the TCAs tested, i.e., amitriptyline, desipramine, and imipramine, showed a marked and reversible inhibition of Kir4.1 channels. They produced a greater inhibition at $+30$ mV than at $-110$ mV, which was similar to the action of nortriptyline. Current ratios in the presence of amitriptyline, desipramine, and imipramine were $0.30 \pm 0.07$ ($n = 5$), $0.14 \pm 0.02$ ($n = 5$), and $0.41 \pm 0.04$ ($n = 4$) at $-110$ mV, respectively, whereas they were $0.09 \pm 0.02$ ($n = 5$), $0.07 \pm 0.01$ ($n = 5$), and $0.17 \pm 0.09$ ($n = 4$) at $+30$ mV, respectively. Thus, it seems likely that TCAs commonly block astroglial $K^+$-buffering Kir4.1 channels in a voltage- and time-dependent fashion similar to nortriptyline.

**Discussion**

The major findings of this study are as follows. The typical TCA nortriptyline inhibits Kir4.1 channels that form the $K^+$ spatial buffering current in brain astrocytes. The inhibition by the drug depends on the voltage difference from $E_K$ and shows time dependence. It becomes stronger and faster as the membrane is depolarized. Other TCAs, such as amitriptyline, desipramine, and imipramine, inhibit Kir4.1 channels in a similar way to nortriptyline.

**The Mechanism of Kir4.1 Blockade.** Nortriptyline reversibly inhibited Kir4.1 currents in a concentration-dependent manner. The $IC_{50}$ value at $-110$ mV was 38 $\mu$M for Kir4.1, whereas it was 246 $\mu$M for Kir2.1 channels. Furthermore, a previous study using *Xenopus* oocytes (Kobayashi et al., 2004) demonstrated that nortriptyline acts as a partial antagonist and only weakly inhibits Kir3.1/3.2 and Kir3.1/3.4 channels ($IC_{50}$ values, 132 and 393 $\mu$M, respectively) with a maximal response of approximately 60 to 65%, whereas it barely inhibits homomorphic Kir3.2 or Kir1.1 channels. There-
fore, the inhibitory action of nortriptyline is relatively specific to Kir4.1 among various Kir channels.

The Hill coefficient for the concentration-response curve of nortriptyline in inhibiting Kir4.1 was nearly unity. This suggests that nortriptyline inhibits Kir4.1 channels through a 1:1 interaction between the drug and the binding site. The inhibition of Kir4.1 channels by nortriptyline was voltage- and time-dependent. The blocking kinetics of nortriptyline could be well fitted with a single exponential curve, suggesting that its inhibitory mechanism can be largely described with a first order reaction independent of channel gating.

The inhibition of Kir4.1 channels by nortriptyline became stronger and faster as the membrane was depolarized. The relationships between $P_o$ and $\tau$ values for the nortriptyline blockade and the membrane potential were both shifted in parallel with changes in $E_K$ when altering $[K^+]_o$ which suggests that the blocking kinetics of nortriptyline are determined not by the membrane voltage itself but by the voltage difference from $E_K$. These characteristics are similar to those of other pore blockers for Kir channels, such as Ba$^{2+}$, Cs$^+$, polyamines, and ammonium derivatives, although Ba$^{2+}$ and Cs$^+$ inhibit the channel more strongly as the membrane is hyperpolarized (Hagiwara et al., 1976, 1978; French and Shoukimas, 1985; Oliver et al., 1998). Because $P_o$ increased and $\tau$ for nortriptyline inhibition decreased with elevating $[K^+]_o$ at given membrane potentials, extracellular K$^+$ might selectively displace the drug from its blocking site for example through electrostatic repulsion. This may occur not only at extracellular sites but also at intracellular action site of the drug as in the cases of ammonium derivatives and polyamines (Armstrong, 1971; Shapiro, 1977; Oliver et al., 1998).

The depolarization-enhancing inhibitory effects of nortriptyline mimicked the actions of internally applied Cs$^+$, Li$^+$, organic cations (e.g., tetrabutylammonium, D-glucose-ammonium, and N-methylstrychnine), and polyamines on K$^+$ channels in various preparations (Shapiro, 1977; French and Shoukimas, 1985; Oliver et al., 1998). It is therefore conceivable that nortriptyline inhibits Kir4.1 channels from the...
inside after permeating into the cells. This possibility is supported by the recent finding that externally applied imipramine can easily cross the cell membrane in its uncharged form and cause a voltage-dependent blockade of hEag1 K⁺ channels by acting from the inside in its charged form (Garcia-Ferreiro et al., 2004).

Therefore, in this context, we estimated the parameter of electrical distance (μ) for the drug-binding site within Kir4.1 channels with the kinetic data from Fig. 4, according to the following equation (French and Shoukimas, 1985):

$$K_d(V) = K_0 \exp(-z\mu F V/RT)$$

(7)

where $K_d(V)$ and $K_0$ are the $K_d$ at different membrane voltage and 0 mV, respectively, $z$ is the charge of the blocking agent, and $RT/F$ is 25 at 22°C. Given that nortriptyline has a single protonation site ($z = 1$), the $μ$ value of nortriptyline was estimated as 0.62, implying that nortriptyline might pass 62% of the electrical field from the inside across the membrane before reaching its blocking site. This $μ$ value was considerably higher than those of other organic cations (e.g., tetrabutylammonium, 0.15; $p$-glucose-ammonium, 0.36; and N-methylstrychnine, 0.18 from the inside) in inhibiting squid axon K⁺ channels (French and Shoukimas, 1985) and also that of imipramine (0.39 from the inside) in inhibiting hEag1 K⁺ channels (Garcia-Ferreiro et al., 2004). Interestingly, the $μ$ value of nortriptyline was close to that of strychnine (0.62) for K⁺ channels in the frog node of Ranvire (Shapiro, 1977), where externally applied strychnine inhibited the K⁺ channels from inside of the plasma membrane in a voltage-dependent manner. Thus, our results suggest that nortriptyline acts as a blocker for Kir4.1 channels by binding at a deep binding site. Further studies are required to determine the precise mechanism and site of action of nortriptyline in inhibiting Kir4.1 channels.

Possible Functional Role of Kir4.1 Blockade by Nortriptyline. Like nortriptyline, other TCAs (i.e., amitriptyline, imipramine, and desipramine) inhibited Kir4.1 currents in a voltage-dependent fashion. These observations suggest that the astroglial Kir4.1 channels could be a common target for TCAs. Although the $K_d$ value of nortriptyline (28.3 μM at $E_K$) was considerably higher than the clinical plasma concentrations of TCAs (e.g., nortriptyline, 0.2–0.6 μM; amitriptyline, 0.4–0.9 μM; imipramine, 0.7–1.1 μM; desipramine, 0.5–1.1 μM) (Baldessarini, 2001; Kobayashi et al., 2004), it is known that cerebral concentrations of TCAs reach values much higher than those in the plasma due to their high brain/plasma distribution ratios of 10:1 to 30:1 (Glotzbach and Preskorn, 1996; Kaster et al., 2005). Alternatively, because TCAs are known to elicit seizure in humans when administered in excess (Montgomery, 2005), neuronal facilitation via the Kir4.1 blockade by TCAs may act in a proconvulsant way at very high doses. Further studies are required to elucidate the clinical relevance of Kir4.1 blockade by TCAs.

Conclusions

This study demonstrated for the first time that nortriptyline and other TCAs cause a concentration-, voltage-, and time-dependent inhibition of astroglial K⁺-buffering Kir4.1 channels and thus suggested the possibility that TCAs alter the spatial K⁺ buffering in the brain. Although the clinical relevance of Kir4.1 blockade by TCAs is still unclear at present, further studies with other types of antidepressants such as the selective serotonin reuptake inhibitors may help understanding the potential roles of functional alteration of astroglial Kir4.1 channels in the brain.

Acknowledgments

We thank S. Hirose (Fukuoka University) for kindly providing human Kir4.1 plasmid DNA, Ian Findlay (Tour University, France) for critical reading of the manuscript, and C. Tsuzuki for excellent technical assistance.

References


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