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# Block of rat brain recombinant SK channels by tricyclic antidepressants and related compounds

John C. Dreixler, Jing-Tan Bian, Ying-Jun Cao, Michael T. Roberts, Jeffrey D. Roizen, Khaled M. Houamed *

*Department of Anesthesia and Critical Care, University of Chicago, 5841 S. Maryland Ave., Box 4028, Chicago, IL 60637, USA*

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**Abstract**

SK channels are small conductance, $Ca^{2+}$-activated $K^+$ channels that underlie neuronal slow afterhyperpolarization and mediate spike frequency adaptation. Using the patch clamp technique, we tested the effects of eight clinically relevant psychoactive compounds structurally related to the tricyclic antidepressants, on SK2 subtype channels cloned from rat brain and functionally expressed in the human embryonic kidney cell line, HEK293. Amitriptyline, carbamazepine, chlorpromazine, cyproheptadine, imipramine, tacrine and trifluperazine blocked SK2 channel currents with micromolar affinity. The block was reversible and concentration-dependent. The potency differed according to chemical structure. In contrast, the cognitive enhancer linopirdine was ineffective at blocking these channels. Our results point to a distinct pharmacological profile for SK channels. 

*Keywords:* $K^+$ channel; Calcium; Calmodulin; Patch clamp; Antipsychotic; Dequalinium

## 1. Introduction

Small conductance $Ca^{2+}$-activated $K^+$ channels (SK channels) are characterized by their small unitary conductance, membrane voltage-independent gating, and exquisitely high sensitivity to activation by intracellular $Ca^{2+}$ ($[Ca^{2+}]_i$), their natural ligand (Vergara et al., 1998). Activation of neuronal SK channels underlies the slow afterhyperpolarization and mediates the phenomenon of spike frequency adaptation, which converts a tonically firing neuron to phasic behavior (Sah, 1996). Underscoring the importance of SK channels in behavior are the effects of apamin injection into the brain. This specific SK channel blocker causes long-term sleep disturbances, hyper-excitability, profound changes in learning ability and neurodegeneration (Behnisch and Reymann, 1998; Gandolfo et al., 1996; Ghelardini et al., 1998; Heurteaux et al., 1993). Recent reports have also linked polymorphisms in SK channel genes to bipolar disorder, epilepsy and schizophrenia (Chandy et al., 1998; Dror et al., 1999; Sander et al., 1999; Verma-Ahuja et al., 1995).

SK channel-mediated afterhyperpolarization in central neurons is blocked by tricyclic compounds structurally related to antidepressants (Dinan et al., 1987). Tricyclic compounds also block neuronal voltage-gated $K^+$ channels (Kv channels; Kuo, 1998; Mathie et al., 1998). We have tested the action of eight psychoactive tricyclic compounds and a cognitive enhancer on SK2 channels cloned from rat brain (rSK2). This SK channel subtype is widely expressed in central neurons and may account for most of the apamin binding sites in the brain (Kohler et al., 1996; Stocker et al., 1999). Our results indicate that psychoactive tricyclic compounds potently block rSK2 channels.

## 2. Methods

### 2.1. Cells

Experiments were performed on recombinant rSK2 channels (Kohler et al., 1996) permanently expressed in a human embryonic kidney-derived cell line, HEK293. The

* Corresponding author. Tel.: +1-773-702-7552; fax: +1-773-702-4791.

*E-mail address:* khouamed@midway.uchicago.edu (K.M. Houamed).

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cell line (provided by Drs. W. Joiner and L. Kaczmarek, Yale University) was generated by transfecting HEK293 cells with a plasmid construct encoding the rSK2 sequence and a geneticin-resistant gene contained within the mammalian expression vector pcDNA 3.0 (Invitrogen). Geneticin-resistant colonies were clonally purified, propagated and tested for rSK2 expression by patch clamp. Control, untransfected HEK293 cells were obtained from American Type Culture Collection. The cells were grown in minimal essential medium supplemented with 10% fetal calf serum, antibiotics (penicillin and streptomycin), sodium pyruvate and the glutamine substitute Glutamax (Life Technologies). The cells were incubated at 37°C in a water-saturated 5% $CO_2$ atmosphere and passaged 1–2 times weekly. The cells were plated on 35-mm Falcon 3001 plastic petri dishes 1–2 days before experiments.

### 2.2. Electrophysiology

Experiments were performed at room temperature (25°C) using the whole-cell variant of the patch-clamp technique. Patch pipettes were pulled from thin-wall borosilicate glass, wax coated and fire polished to have tip resistance of 4–10 MΩ when filled with an intracellular solution composed of (in mM): 137.5 $KMeSO_4$, 1 $MgCl_2$, 3 EGTA, 10 HEPES, 2 $CaCl_2$, 3 ATP, 5 glucose; pH, 7.3. The ~1 μM calculated free calcium ion concentration ($[Ca^{2+}]$) of this solution is sufficient for maximal activation of rSK2 channels (Kohler et al., 1996). The cell under study was continuously perfused, using a rapid local microperfusion device, with a modified Ringer's solution composed of (in mM): 117 NaCl, 30 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 HEPES, 2 $NaHCO_3$, 5 glucose; pH 7.4. The microperfusion device consisted of a 500-μm-diameter glass pipette connected, via a 10:1 manifold and valves, to reservoirs containing test solutions. The outlet of the microperfusion device was mounted on a micromanipulator and maneuvered to within 100 μm of the cell under study; the time constant for exchange of this system was ~1 s. Drugs were dissolved in the modified Ringer's solution and applied for 30 s using this device. The recording chamber was also continuously perfused with a modified mammalian Ringer's solution.

The cells were voltage clamped at −100 mV holding potential. The potassium reversal potential under our conditions was ~−41 mV. Activation of rSK2 channels could be observed as a sustained inward current as the

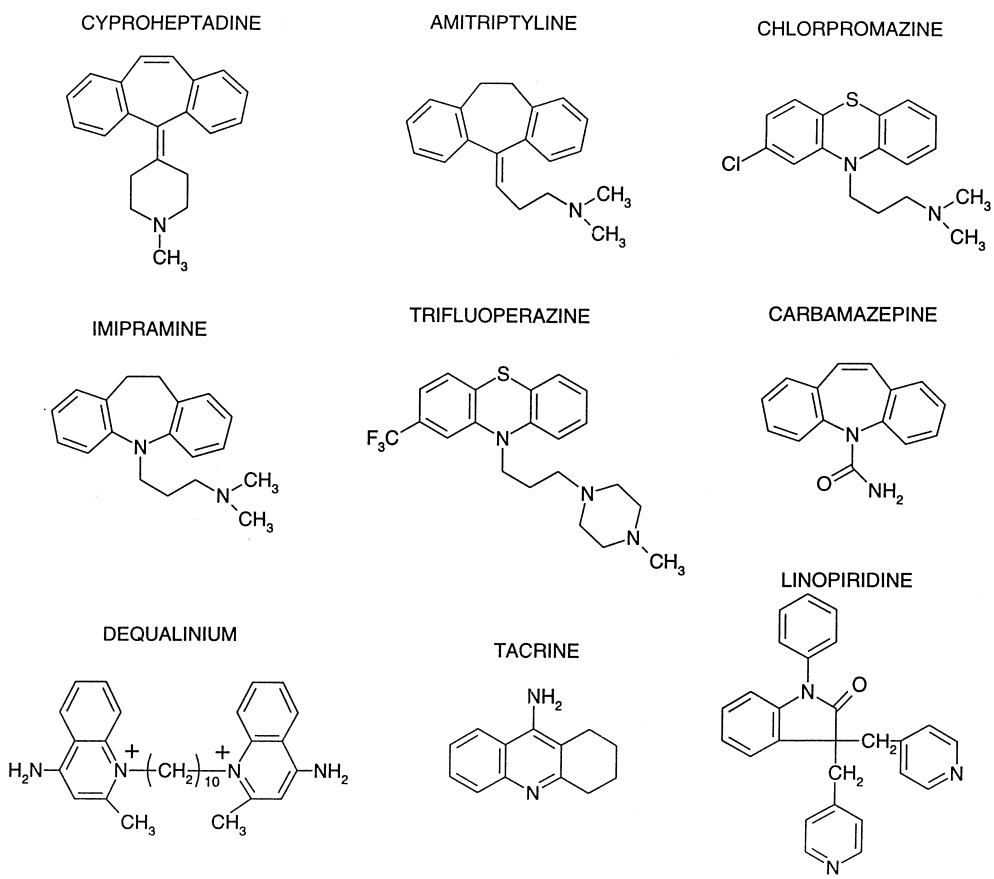


Fig. 1. The chemical structures of the drugs used in this study.

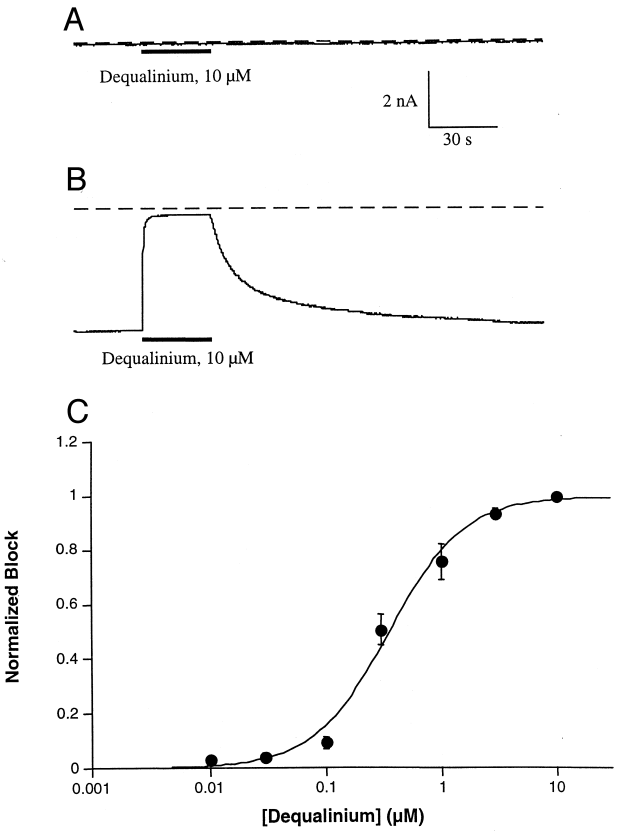


Fig. 2. Block of rSK2 channel currents by dequalinium. Membrane current recordings in identical conditions of (A) a whole-cell clamped control, non-transfected HEK293 cell and (B) an HEK293 cell permanently expressing recombinant rSK2 channels. The cells were clamped at −100 mV; the SK current is inward (dashed line indicates the zero holding current level). The block by 10 μM dequalinium (solid bar) is potent and reversible. (C) Fitted dose response curve of dequalinum block. Each point is the mean (±S.D.) of recordings from six to seven cells. The block at each drug concentration is normalized to the block by 10 μM dequalinum in the same cell.

interior of the cell equilibrated with the high $[Ca^{2+}]$ pipette solution. The block by test drugs, measured as the decrease in the inward membrane current, was internally normalized to the block evoked by a 30-s application of 10 μM dequalinium. The normalized block (mean ± S.D.) was semilogarithmically plotted against drug dose and least-squares fitted to the equation:

$$I = I_{max} / \left[1 + (K_D / C)^n\right] \quad (1)$$

where '$I$' is the inhibition (block), relative to the maximal inhibition ($I_{max}$) achieved at drug dose '$C$', '$K_D$' is the apparent equilibrium dissociation constant and '$n$' is the Hill coefficient.

### 2.3. Chemicals and drugs

All salts used in this study were purchased from Fluka or Sigma, except $KMeSO_4$ (Pfaltz and Baur), and ATP (ICN). The structures of the drugs used in this study are shown in Fig. 1. All drugs were from Sigma except linopirdine (DUP 996), which was from Research Biochemicals. The drug stock solutions were made up either in water or dimethyl sulfoxide (DMSO). The highest drug doses contained up to 1% v.v. DMSO. In control experiments we have verified that DMSO, at up to 4%, did not affect rSK2 currents or the membrane electrical properties in HEK293 cells (unpublished observation).

## 3. Results

### 3.1. SK2 channel expression

Dialysis of rSK2-expressing HEK293 cells evoked a large standing inward membrane current. This current was not observed in cells dialyzed with nominally zero $[Ca^{2+}]$ pipette solutions nor in control, non-transfected HEK293 cells (Fig. 2A; unpublished observations). The current reversed at ∼ −41 mV, the calculated potassium equilibrium potential; it was blocked by the SK channel blockers apamin and dequalinium (Fig. 2B; unpublished observations). Taken together, these observations indicate that rSK2 channel activation underlies this current.

### 3.2. Dequalinium

The bis-quinolinium ganglionic blocker dequalinium, tested in the 10 nM–10 μM dose range, blocked rSK2

Table 1

| Drug | Number of cells tested | Concentration range (μM) | Fitted $K_D$ (μM) | Fitted $n$ |
|---|---|---|---|---|
| Amitriptyline | 5–9 | 0.1–300 | 54.79 | 0.93 |
| Carbamazepine | 5–10 | 0.1–100 | 14.45 | 0.93 |
| Chlorpromazine | 7–9 | 0.1–100 | 12.75 | 1.24 |
| Cyproheptadine | 5–6 | 0.1–300 | 15.27 | 0.96 |
| Dequalinium | 6–7 | 0.01–10 | 0.354 | 1.33 |
| Imipramine | 5–7 | 1–300 | 21.69 | 0.99 |
| Linopirdine | 3–6 | 2–200 | – | – |
| Tacrine | 6–9 | 10–1000 | 53.7 | 1.66 |
| Trifluperazine | 5–9 | 0.1–100 | 7.6 | 0.86 |

channel currents reversibly and dose-dependently (six to seven cells). Fig. 2B illustrates the time course of block and recovery of rSK2 channel currents by a saturating dose of dequalinium. Eq. (1) was fit to the normalized block by dequalinium to yield $K_D = 354$ nM and $n = 1.33$ (Fig. 2C; Table 1). Because of the potency and the ready reversibility of block by dequalinium, we used a supermaximal blocking concentration (10 μM) of this compound to internally normalize the block by the other drugs used in this study.

### 3.3. Tricyclic drugs

All seven psychoactive tricyclic compounds tested in this study blocked rSK2 channel currents dose-dependently, reversibly and completely (Fig. 3A for imipramine). However, the fitted equilibrium constants varied by sevenfold (Fig. 3B and C; Table 1).

The most potent tricyclic blockers were the antipsychotic phenothiazines, trifluperazine and chlorpromazine. Trifluperazine was tested in the dose range 0.1–100 μM

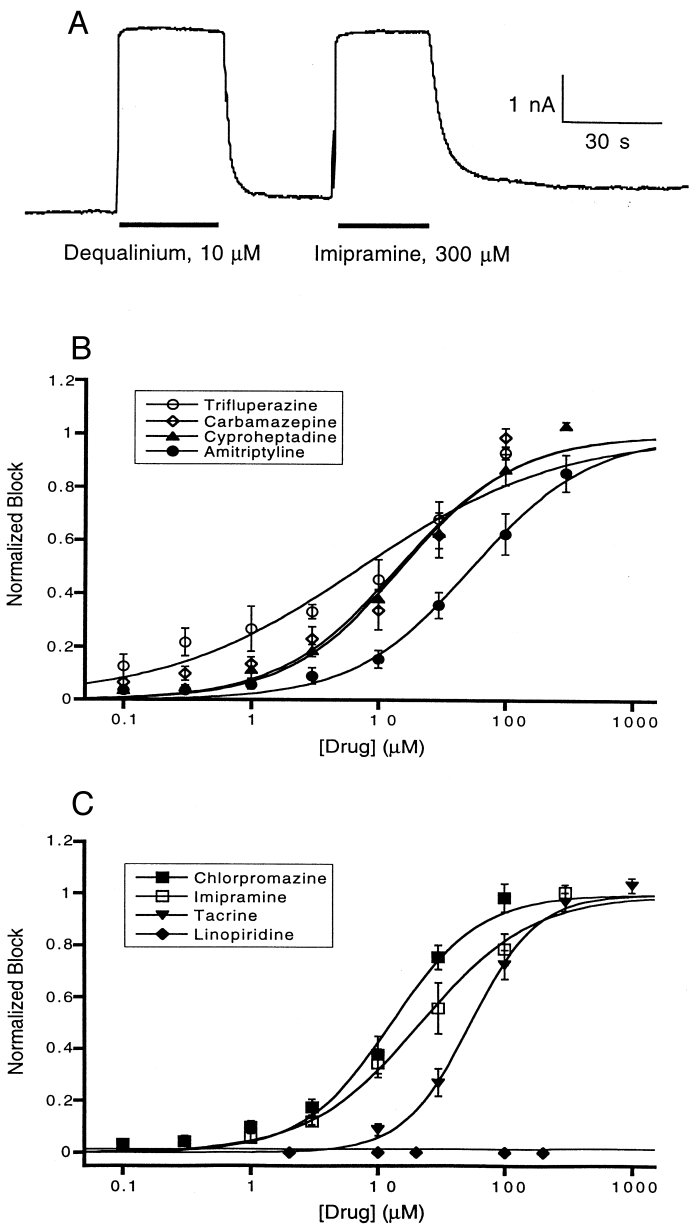


Fig. 3. Block of rSK2 channel currents by tricyclic compounds. (A) Membrane current recording in an HEK293 cell permanently expressing recombinant rSK2 channels. The cell was whole-cell clamped at −100 mV. Dequalinium (10 μM) and imipramine (300 μM) were applied at the time indicated by the horizontal bars. The inward rSK2 current was rapidly and reversibly blocked (dashed line indicates the zero holding current level). (B) Fitted dose response curves of drug block by trifluperazine, carbamazepine, cyproheptadine and amitriptyline. (C) Inhibition of rSK2 currents by chlorpromazine, imipramine, tacrine, and linopiridine. Each point is the mean (±S.D.) of recordings from three to 10 cells. The block at each drug concentration is normalized to the block by 10 μM dequalinum in the same cell.

on five to nine cells. The fitted $K_D$ was 7.6 μM and $n$ was 0.86. The same dose range of chlorpromazine was tested on seven to nine cells. It blocked rSK2 currents with $K_D = 12.75$ μM and $n = 1.24$. The anticonvulsant carbamzepine in the 0.1–100 μM dose range was tested on 5 to 10 cells. It blocked with a $K_D = 14.5$ μM and $n = 0.93$. The antihistamine cyproheptadine tested in the dose range 0.1–300 μM on five to six cells was similarly potent at blocking SK2 channel currents ($K_D = 15.3$ μM; $n = 0.96$). The antidepressant imipramine was tested in the dose range 1–300 μM on five to seven cells; it blocked rSK2 channel currents with $K_D = 21.7$ μM, $n = 0.99$. Amitriptyline, a closely related antidepressant, blocked rSK2 channel currents with $K_D = 54.8$ and $n = 0.93$; it was tested in the dose range 0.1–300 μM on five to nine cells. The cognitive enhancer tacrine (9-amino-1,2,3,4-tetrahydroacridine) blocked rSK2 channel currents when tested in the 10 μM–1 mM concentration range on six to nine cells. The curve fit to the dose-block data yielded a $K_D = 53.7$ μM and $n = 1.66$.

### 3.4. Linopirdine

The cognitive enhancer linopirdine (DUP 996) was without effect in the dose range tested (2–200 μM; three to six cells).

## 4. Discussion

This study shows that rSK2 channels, like their native neuronal counterparts, are potently and reversibly blocked by dequalinium. The 354 nM $K_D$ reported in this study is similar to the ~600 nM potency of this drug at blocking native SK channels in sympathetic neurons (Dunn et al., 1996), as well as recombinant SK channels (Strobaek et al., 2000). We have used dequalinium as our standard blocker in this study because of its high potency and rapid reversibility.

This study also shows, for the first time, that recombinant rSK2 channels, like certain other native and recombinant potassium channel subtypes, are potently blocked by psychoactive tricyclic compounds and related molecules. Seven out of the eight psychoactive compounds tested blocked rSK2 channels with micromolar affinity; the eighth, linopirdine (DUP 996), was completely without effect at the concentration range tested.

The phenothiazines, chlorpromazine and trifluperazine, blocked rSK2 channels with 12.8 and 7.6 μM apparent affinity, respectively. Thus, rSK2 channel currents are approximately threefold more sensitive to trifluperazine block than the SK channel-mediated slow afterhyperpolarization in hippocampal CA1 neurons (Agopyan and Krnjevic, 1993). Likewise, micromolar concentrations of both chlorpromazine and trifluperazine have been shown to block neuronal Kv channels and large conductance calcium-activated potassium channels [BK channels; (Ikemoto et al., 1992; Lee et al., 1997; Mathie et al., 1998; Nakazawa et al., 1995)].

The antiepileptic drug carbamazepine, at a concentration range that overlaps with its therapeutic dosage, blocks rSK2 channels with a 14.5 μM apparent dissociation constant. To our knowledge, this is the first report on the effects of carbamazepine on SK channels. Moreover, it appears that carbamazepine shows some selectivity towards SK channels since it has been reported to be ineffective at blocking BK and Kv channels (Kuo, 1998; Lee et al., 1997; Wooltorton and Mathie, 1993; Zona et al., 1990). Our results, compared to previous studies, indicate that carbamazepine blocks rSK2 channels up to 10 times more potently than neuronal $Na^+$ channels (McLean and Macdonald, 1986; Schwarz and Grigat, 1989; Willow et al., 1985). Since this drug blocks rSK2 channels substantially at concentrations overlapping with its therapeutic range [10–20 μM; (Zona et al., 1990)] this block may be responsible for part of its clinical effects or side effects.

Cyproheptadine is an histamine $H_1$ receptor and 5-$HT_2$ receptor antagonist that also blocks neuronal Kv channels (Mathie et al., 1998; Wooltorton and Mathie, 1993, 1995). In our study, this drug blocked rSK2 channels with $K_D \sim 15$ μM (Fig. 3B). Our study is the first to report that this drug can block native or recombinant SK channels. This result contrasts with the finding that this compound *enhanced* the SK-channel mediated slow afterhyperpolarization in hippocampal neurons (Gurevich et al., 1990). A possible explanation is that cyproheptadine removes a tonic inhibition of native channels by 5-HT receptors.

The antidepressants amitriptyline and imipramine blocked rSK2 channels with $K_D$s = 55 and 22 μM, respectively. Therefore, these drugs are equally potent at blocking rSK2 channels and native neuronal BK and Kv channels (Kuo, 1998; Lee et al., 1997; Wooltorton and Mathie, 1993, 1995).

We have observed that the anticholinesterase cognitive enhancer tacrine blocks rSK2 channels with ~54 μM potency. This is almost identical to the potency of this drug at blocking several different neuronal Kv channel types (Halliwell and Grove, 1989; Robbins and Sim, 1990; Rogawski, 1987; Wooltorton and Mathie, 1993).

Linopirdine (DUP 996) is a novel cognitive enhancer that has been reported to exert its effects through blocking a presynaptic Kv channel current, probably the 'M' current, leading to increased release of acetylcholine (Aiken et al., 1995). This drug has been reported to either block (Schnee and Brown, 1998) or spare (Aiken et al., 1995; Lamas et al., 1997) the slow afterhyperpolarization current mediated by native neuronal SK channels. In our study this drug, up to its 200 μM aqueous solubility limit, was completely inactive at blocking rSK2 channels. A possible explanation for this discrepancy is that linopirdine may selectively block certain SK channel subtypes other than rSK2.

We have shown that rSK2 channels are blocked by six clinically relevant, psychoactive tricyclic drugs. It would be of interest to investigate the SK channel subtype selectivity of these drugs and to determine whether these drugs block rSK2 channels through a common mechanism. Previous work on the mechanisms of block by tricyclic compounds has shown that these compounds block Kv channels in a gating state-dependent manner (Kuo, 1998). The drugs blocked only when applied extracellularly (Kuo, 1998; Wooltorton and Mathie, 1995). The potency of tricyclic compounds at blocking depends on the external pH (Mathie et al., 1998; Wooltorton and Mathie, 1995). Since these compounds are weak bases they exist in both charged and uncharged forms at neutral pH. The blocking potency was found to correlate with the $pK_a$ of the drugs in a manner suggesting that the channels are blocked either solely or more potently with uncharged drug moieties. In our study, however, the potencies of tricyclics at blocking rSK2 channels do not correlate with $pK_a$. Thus, chlorpromazine is more potent than cyproheptadine, which has a lower $pK_a$, and tacrine, which has a higher $pK_a$ (Mathie et al., 1998). Moreover, chlorpromazine and trifluperazine inhibit calmodulin. Calmodulin associates constitutively and $Ca^{2+}$-independently with SK channels where it acts as the $Ca^{2+}$ sensor for channel activation (Xia et al., 1998). Chlorpromazine and trifluperazine may therefore act allosterically through calmodulin to affect SK channel gating. It has, however, been shown that the interaction of calmodulin with this channel is relatively insensitive to calmodulin antagonists (Fanger et al., 1999; Xia et al., 1998).

In conclusion, our studies indicate that tricyclic compounds may be useful pharmacological probes for studying recombinant SK channels. This utility may be extended to characterizing the pharmacological properties of other recombinant SK channel subtype, and relating them to native neuronal SK channels.

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