TEDISAMIL POTENTLY BLOCKS POTASSIUM OUTWARD CURRENTS IN ASTROCYTES FROM MOUSE (MUS MUSCULUS) PRIMARY CULTURE.

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Astrocytic active role in potassium (K^+) homeostasis through high K^+ membrane permeability and "spatial" buffering is well established (Hertz, 1986, Ann. N.Y. Acad. Sci., 481:318). Astrocytes are known to express outward K^+ currents (Bevan and Raff, 1985, Nature, 315: 229; Nowak et al., 1987, J. Neurosci., 7: 101). In this report the whole cell patch-clamp technique has been used to characterize the effect of KC 8857 (tedisamil) on K^+ outward currents in mouse cultured astrocytes.

Astrocytes were prepared as described by Hertz et al., 1985, in Neuromethods, AA Boulton and GB Baker eds., Humana Press, Clifton, NJ, vol.1, pp.117-167. The K^+ currents were recorded using patch-clamp electrodes filled with (in mM): 120 KCl, 15 EGTA and 5 MgATP. Superfusion solution was composed of (in mM): 137 NaCl, 5.4 KCl, 1 $MgCl_2$, 10 glucose and 2 $CaCl_2$, 10 HEPES (pH 7.4). Two types of K^+ currents were observed in cortical astrocytes. Tedisamil (KC8857) is a new highly selective blocker of K^+ channels in heart (Dukes and Morad, 1989, Am. J. Physiol., 257:H1746). We examined, therefore, whether tedisamil might modulate the transient and delayed rectifier type astrocyte K^+ channels. Figure 1 shows the effect of 10 uM tedisamil on the slowly activating K^+ channel. Wash-in of tedisamil dramatically reduced the magnitude of this current by an apparent acceleration of the inactivation rate of the current.

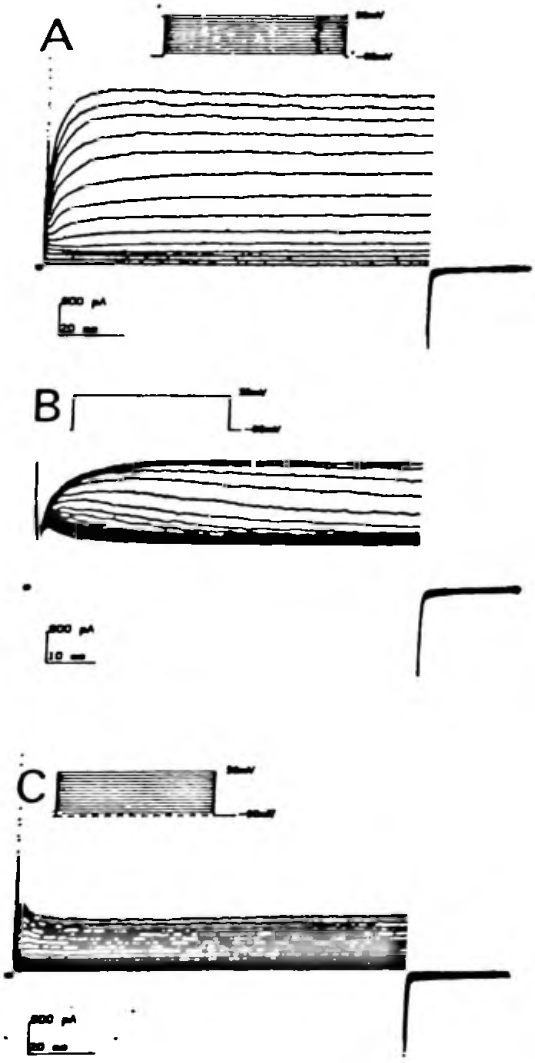

Figure 1. Tedisamil blocks the slowly activating outward K^+ channel. A panel, control; B panel, wash-in of 10 uM tedisamil; C panel, final effect of 10 uM tedisamil. Each panel shows the membrane current recorded during 120 ms voltage clamp depolarizations from a holding potential of -80 mV. Panels A and C were recorded under steady state conditions with 10 mV increments of the clamped membrane potential in the range from -70 mV to +50 mV. Panel B was recorded with consecutive depolarizations, all to +20 mV, during wash-in of tedisamil.

Figure 2 shows the effect of 10 uM tedisamil in an astrocyte expressing both transient and delayed rectifier type outward currents. Wash-in of tedisamil blocked both the rapid and slowly activating currents, again by a enhancing the kinetics of the inactivation. The effect of tedisamil on the astrocyte K^+ channels is similar to its effect on cardiac K^+ channels suggesting that the drug has a common site of action at K^+ channels of cardiac and neuronal cells.

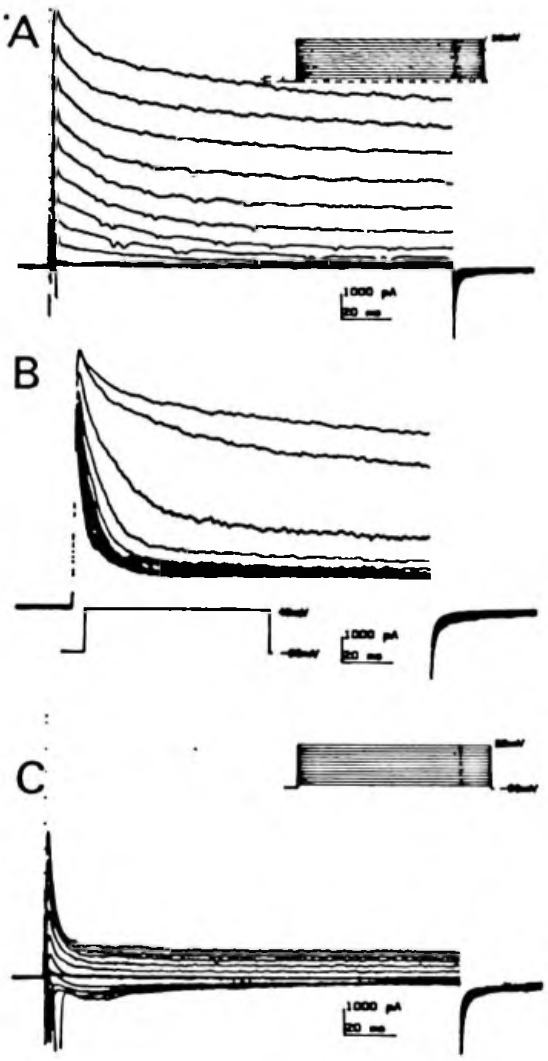

Figure 2. Tedisamil blocks the rapidly inactivating outward K^+ current. A panel, control; B panel, wash-in of 10 um tedisamil; C panel, final effect of 10 uM tedisamil. All panels show membrane currents recorded during 150 ms voltage clamp depolarizations from a holding potential of -80 mV. Panels A and C show the voltage dependence of the current measured with 10 mV increments in the range from -70 mV to +50 mV. Panel B was measured during wash-in of the drug with consecutive depolarizations to +50 mV.

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