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Research Report

Actions of bis(7)-tacrine and tacrine on transient potassium current in rat DRG neurons and potassium current mediated by $K_V4.2$ expressed in *Xenopus* oocyte

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ABSTRACT

Bis(7)-tacrine [bis(7)-tetrahydroaminacrine] is a dimeric AChE inhibitor derived from tacrine with a potential to treat Alzheimer's disease. Actions of bis(7)-tacrine on ligand-gated ion channels and voltage-gated cation channels have been identified on neurons of both central and peripheral nervous systems. In the present study, the effect of bis(7)-tacrine was investigated on the $K_V4.2$ encoded potassium currents expressed in *Xenopus* oocytes and the transient A-type potassium current ($I_{K(A)}$) on rat DRG neurons. Bis(7)-tacrine suppressed recombinant Kv4.2 potassium channels in a concentration-dependent manner, with IC_{50} value of 0.53 ± 0.13 μM. Tacrine also inhibited Kv4.2 channels, but with a much lower potency (IC_{50} 74 ± 15 μM).The possible mechanisms underlying the inhibition on potassium currents by bis(7)-tacrine/tacrine could be that inactivation of the transient potassium currents was accelerated and recovery of the native or Kv4.2 expressed potassium currents was suppressed by bis(7)-tacrine/tacrine.

1. Introduction

Bis(7)-tacrine [bis(7)-tetrahydroaminacrine], a dimeric acetylcholinesterase (AChE) inhibitor, is composed of two tacrine molecules linked by a heptylene chain (Pang et al., 1996) (Fig. 1). Bis(7)-tacrine is more potent (up to 150-fold) and more selective (around 250-fold) to inhibit AChE (Wang et al., 1999) than tacrine, one of the first-generation anticholinesterasic drugs for palliative treatment of Alzheimer's disease (AD) (Krall et al., 1999). Recently, bis(7)-tacrine has been found to target many kinds of ligand-gated ion channels, for example, bis(7)-tacrine inhibited functions of $GABA_A$ receptors in rat hippocampal neurons (Li et al., 1999), nACh receptors in the *Torpedo* electric organ (Ros et al., 2001), 5-HT_3 receptors in rat trigeminal ganglion neurons (Luo et al., 2004), NMDA receptors in rat hippocampal neurons (Li et al., 2005).

As for the voltage-gated ion channels, tacrine has been reported to suppress the function of voltage-dependent potassium channel in rat hippocampal neurons (Rogawski, 1987; Halliwell and Grove, 1989; Li and Hu, 2002a,b), *Myxicola*

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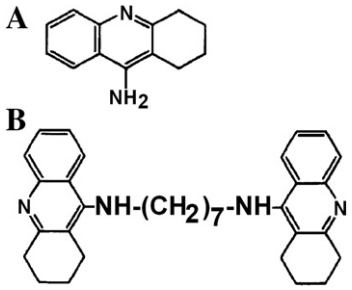

Fig. 1 – The chemical structure of tacrine (9-amino-1,2,3,4-tatrahydroacridine) (A) and bis(7)-tacrine (bis(7)-tetrahydroaminacrine) (B).

giant axon (Schauf and Sattin, 1987) and larval muscles of *Drosophila* (Kraliz and Singh, 1997).

Our recent works identified that bis(7)-tacrine inhibited both delayed rectifier potassium channels in rat DRG neurons and Kv1.2 encoded potassium channels expressed in *Xenopus* oocytes (Nie et al., 2007). In the present work, we have investigated the actions of bis(7)-tacrine on K_V4.2 potassium channels expressed in *Xenopus* oocytes and transient A-type potassium channel in rat dorsal root ganglion (DRG) neurons.

2. Results

2.1. *Bis(7)-tacrine and tacrine suppressed transient potassium currents in K_V4.2-expressing oocytes*

K_V4.2 α-subunits belong to Shal family of potassium channels that tetramerize to form a channel characterized by a transient A-type K^+ current ($I_{K(A)}$). In order to investigate the actions of bis (7)-tacrine and tacrine on $I_{K(A)}$, we used *Xenopus* oocytes expression system to recombine Kv4.2 potassium channel. After 48 hours incubation following K_V4.2 cRNA injection, the outward potassium currents could be recorded in the *Xenopus* oocytes with a step-up depolarization protocol, i.e., the membrane potential was pre-hyperpolarized from −50 mV to −110 mV for 100 ms, and then depolarized from −40 to +80 mV (10 mV increment each step, duration 200 ms), and then restored to original depolarizing potential (H.P.) −50 mV (Fig. 2A, top panel). The activation of outward potassium currents was very fast (about 5 ms at a depolarizing potential +80 mV), while the decay phase of the current reached to a steady state in about 200 ms (Fig. 2A). 4-AP (1 mM) suppressed the transient outward current by 82.6 ± 17.2% (n=6, P<0.05) (Fig. 2A, bottom panel). The activation threshold voltage of

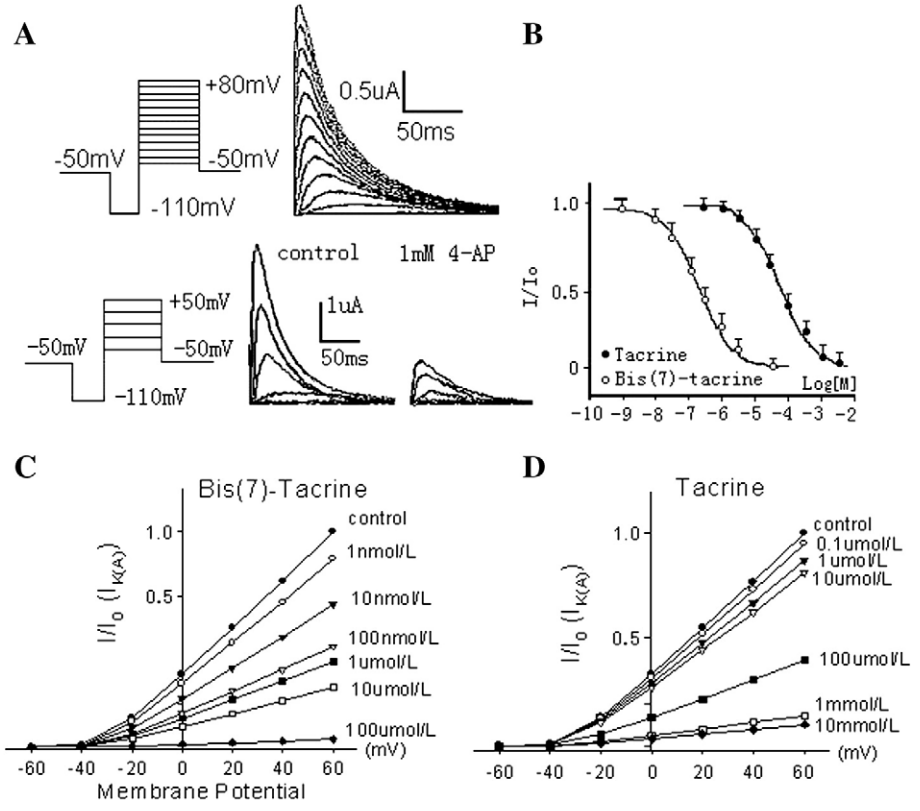

Fig. 2 – Effect of tacrine and bis(7)-tacrine on transient outward potassium currents mediated by K_V4.2-encoded channels expressed in Xenopus oocytes. (A) A series of transient outward currents traces were recorded from *Xenopus* oocytes expressed K_V4.2-encoded potassium channel ($I_{K(KV4.2)}$) based on the protocol shown on the top left. 4-AP (1 mM) suppressed the transient outward current markedly (right panel). (B) Both tacrine and bis(7)-tacrine suppressed $I_{K(KV4.2)}$ in a concentration-dependent manner and IC_{50} values were 74±15 μM (n=17, P<0.05) for tacrine and 0.53±0.13 μM (n=19, P<0.05) for bis(7)-tacrine, respectively. (C) Bis(7)-tacrine suppressed I–V curve of $I_{K(KV4.2)}$. (D) Tacrine also suppressed I–V curve of $I_{K(KV4.2)}$, higher concentration of tacrine were required to have similar effect on $I_{K(KV4.2)}$.