I_A recorded at the end of voltage step for 400 msec ($I_{A\text{-late}}$) were 2.60 x10^{-4} M and 2.40 x10^{-5} M, respectively.

Discussion

In the present study, cloperastine concentration-dependently inhibited three types of voltage-gated channel currents in DRN neurons. But the inhibitory effects were much less potent. On the other hand, we have previously found that the IC_{50} value for cloperastine of the GIRK channel activated current was 8.6x10^{-7} M. Therefore, cloperastine is at least 20-fold more potent in inhibiting GIRK channel than these three channels.

Recently, a few substances have been reported to have an inhibitory effect on GIRK channel activated currents. These are fluoxetine, a selective serotonin reuptake inhibitor (SSRI)[9], bupivacaine[10], a local anesthetic, and so on. However, these non-peptide substances are less potent as inhibitor of GIRK channel, since micromolar concentrations are needed to inhibit the GIRK channel-activated currents. Further, our preliminary study revealed that cloperastine at a large concentration of 10^{-4} M had little effect on glycine-induced and NMDA-induced currents in single brain neurons[8]. Judging from the electrophysiological results obtained thus far, cloperastine should be the most potent non-peptide inhibitor of GIRK channel activated currents. In this context, it is reasonable to mention that cloperastine might be useful as a seed compound for developing a more potent inhibitor of GIRK channel activated currents or a potent GIRK channel blocker.

We have previously reported that cloperastine has ameliorating effect on urinary disturbance caused by cerebral infarction in conscious rat[11], and further that it inhibited hyperactivities caused by repetitive methamphetamine administration in mice[12]. The present results support an idea that pharmacological effects of cloperastine on urinary disturbance and methamphetamine-induced hyperactivities might be at least partly due to its GIRK channel blocking effect.

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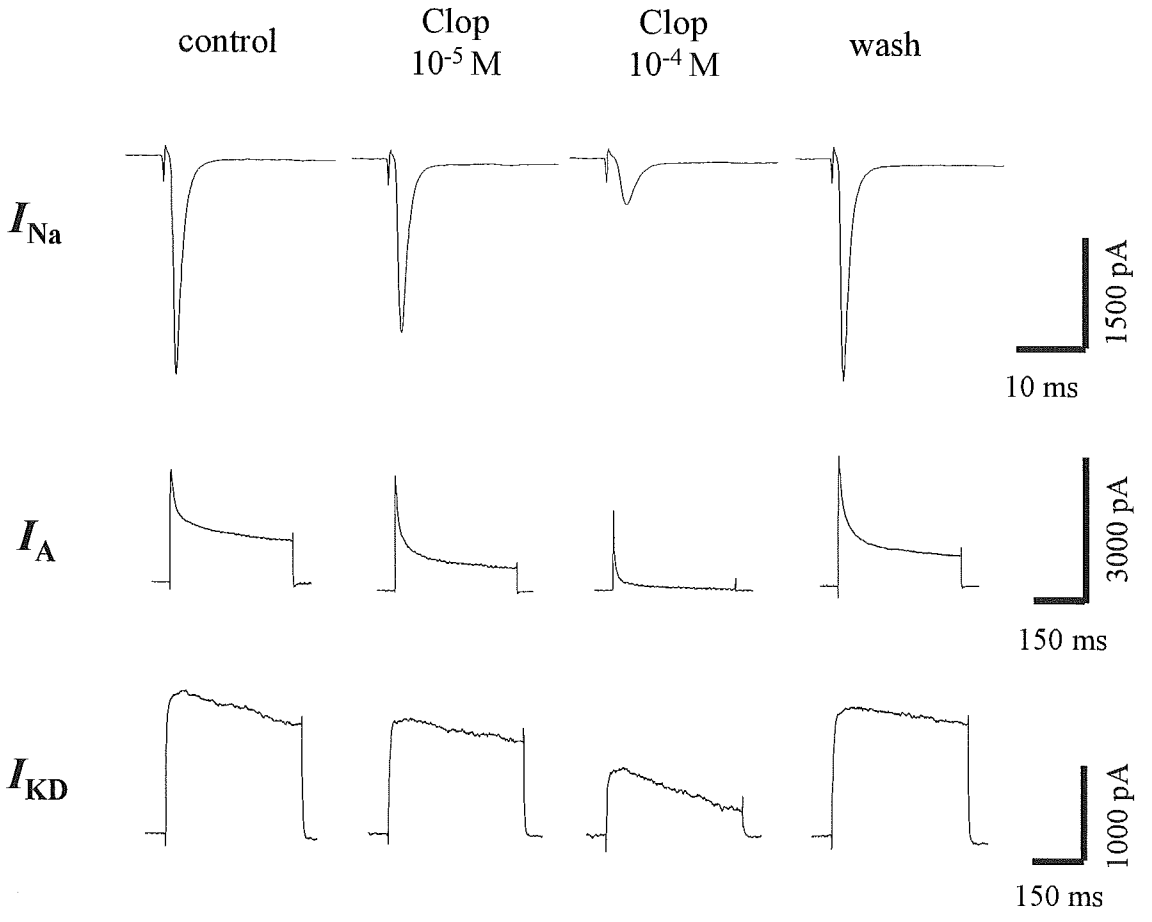
Figure Legends

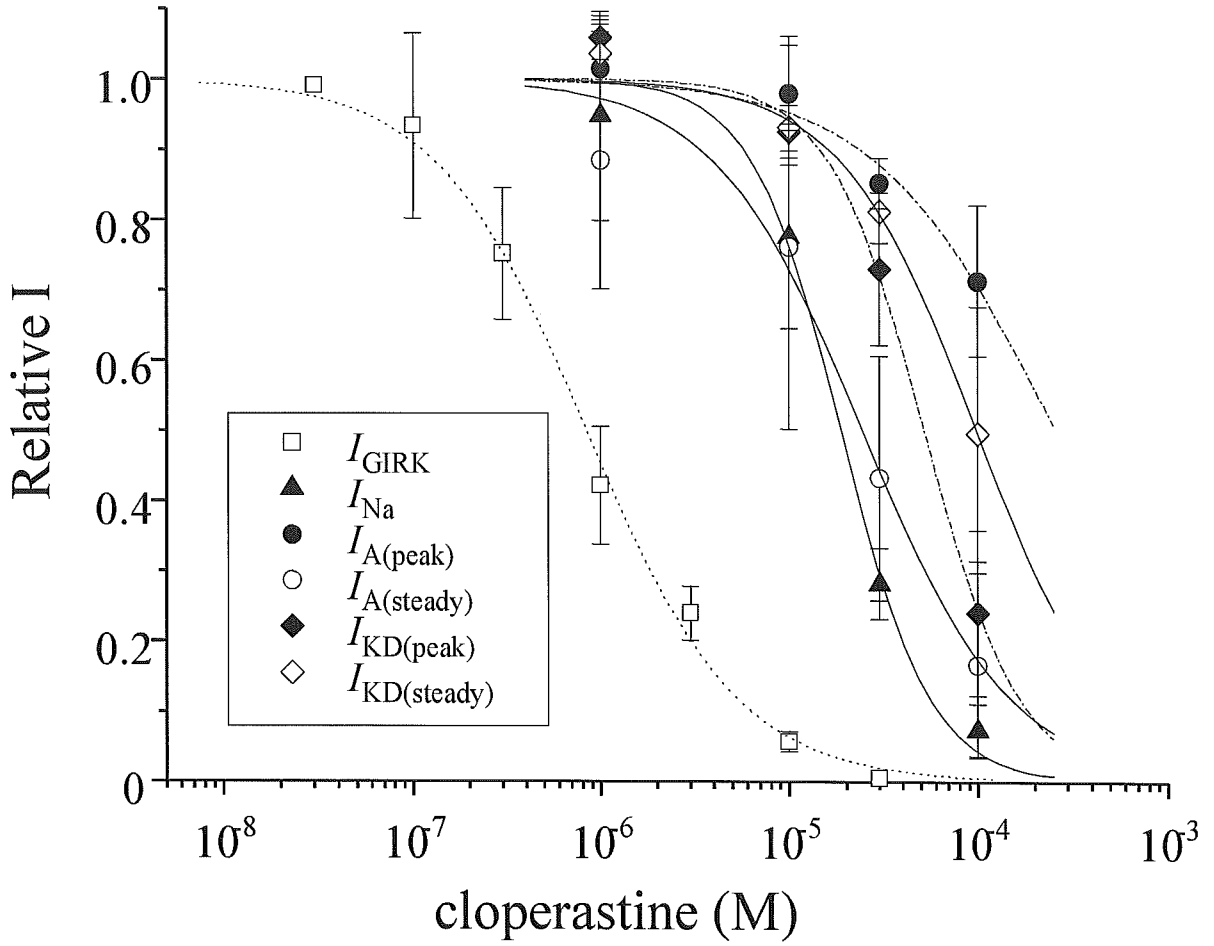
Fig. 1.

Representative current traces of I_{Na}, I_{KD} and I_A in the absence or presence of cloperastine (Clop). I_{Na} was evoked by a voltage step from a holding potential of -80 mV to -20 mV for 50 msec. I_A and I_{KD} were also evoked by a voltage step from a holding potential of -80 mV to 40 mV for 400 msec, respectively.

Fig. 2.

Dose-inhibition relationship showing the effect of cloperastine on I_{Na}, $I_{A\,(peak)}$, $I_{A\,(late)}$, $I_{KD\,(peak)}$ and $I_{KD\,(late)}$. The relationship for the inhibition of cloperastine on 5-HT-induced GIRK channel current was also indicated together for comparison. Data were shown as mean $\pm$ S.E.M. (n = 3).


control
Clop
10-5 M
Clop
10-4 M
wash
INa
1500 pA
10 ms
IA
3000 pA
150 ms
IKD
1000 pA
150 ms


Relative I
1.0
0.8
0.6
0.4
0.2
0
I_{GIRK}
I_{Na}
$I_{A(peak)}$
$I_{A(steady)}$
$I_{KD(peak)}$
$I_{KD(steady)}$
10^{-8}
10^{-7}
10^{-6}
10^{-5}
10^{-4}
10^{-3}
cloperastine (M)

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発行者　主任研究者　高　濱　和　夫
熊本大学大学院医学薬学研究部
環境分子保健学分野
熊本市大江本町5番1号
Tel 096-371-4334

製本　(有)米　田　印　刷
熊本市坪井6丁目21-15
Tel　096-345-0150