S47-4 Novel ameliorating action on cerebral infarction-induced urination disorder of drugs possessing GIRK channel inhibiting action

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We previously reported that centrally-acting antitussives (CAA) inhibited G-protein-coupled inwardly rectifying K^+ (GIRK) channel activated currents in brain neurons. Apart from the above, we have found that CAA affected urination reflex in rats. In this study, we studied whether or not cloperastine (CP) shows ameliorating action on urination reflex disorder associated with cerebral infarction (CI) in rats. Male *Wistar* rats were used. CP at antitussive effective doses ameliorated both parameters of urinary frequency and difficulty in urination. These actions were also found in C57BL/6J mouse model with CI. Next, we carried out micro-dialysis experiments, because monoamines are involved in control of urination reflex, and because GIRKs are coupled to many GPCRs including monoamine receptors. CP increased the levels of noradrenaline, dopamine and serotonin in the prefrontal cortex. The ameliorating actions of CP were reduced by treatment with AMPT but not PCPA, although 8-OH-DPAT improved an increase in urethral resistance associated with CI. The present finding is intriguing that CP at the same antitussive dose ameliorated both parameters of urinary frequency and difficulty in urination. In addition, the finding seems to be important from a point of view of re-profiling of known drugs. Further studies are needed to elucidate mechanisms of the ameliorating action of CP on urination reflex disorder associated with CI.