S05-6 Multiple pharmacological actions of antitussives possessing GIRK channel blocking action in models of intractable brain diseases

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During the course of studies on mechanisms of action of centrally-acting non-narcotic antitussives, we found that the drugs inhibit G protein coupled inwardly rectifying K^+ (GIRK) channel currents in brain neurons. In studies we performed on the basis of this finding, we further found various interesting findings as follows: 1) the drugs at antitussive dose ameliorated both symptoms of urinary frequency and difficulty in urination associated with cerebral infarction in rats. 2) the drugs depressed hyperactivities in methamphetamine-treated or 6-hydoroxydopamin-treated mice. 3) the drugs prevented expression of the brain disrupting action caused by prenatal exposure to DES in mice. 4) the drugs revealed novel antidepressant like action in ACTH-treated rats which are resistant to treatment with various antidepressant drugs developed thus far. 5) Electrophysiological study and NMR analysis suggested that cloperastine, one of antitussives, may have the site of action in the intracellular site of GIRK channels. 6) Micro-dialysis study revealed that the drugs increased the level of noradrenaline, dopamine and serotonin in the prefrontal cortex of rats. Increase in dopamine level was found in the nucleus accumbens. These findings seem to be of interest because these multiplex pharmacological actions were caused at a dose effective to coughing, and because the drugs showed improving and/or therapeutic actions on models of intractable brain diseases resistant to dosing of known drugs. In the symposium, the data are presented addressing antidepressant-like action of the antitussives.