GS5-1 Have compounds possessing GIRK channel blocking action a novel antidepressant effect ?

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Although depression is dramatically increasing, currently available antidepressants are ineffective in 30 % of the patients. We previously found that antitussive drugs inhibited G protein coupled inwardly rectifying K+ (GIRK) channel activated currents. Interestingly, the antitussive drugs ameliorated the symptoms in the models of various intractable brain diseases. We speculate that these effects may be at least due to inhibitory action on GIRK channels. Because various G protein-coupled receptors are coupled to the GIRK channels, it is possible that they may affect the levels of various neurotransmitters in the brain. Therefore, we investigated effects of the drugs on the animal models of depression. Male Wistar rats (150g~330g) were used. Cloperastine (CP) at 40 mg/kg, i.p. and tipepidine (TP) at 20 and 40 mg/kg, i.p. significantly reduced the immobility of rats in the forced swimming test. Interestingly, both drugs also significantly reduced the immobility of ACTH-treated rats which is resistant to antidepressants treatment. Both drugs did not increase locomotor activity. The effects of both drugs in normal and ACTH-treated rats were inhibited by AMPT, but not by PCPA. CP (2.5, 5.0 and 7.5 mg/kg, i.v.) and TP (10 mg/kg, i.v.) significantly increased the levels of serotonin and dopamine in the prefrontal cortex in *in vivo* microdialysis method. Furthermore, TP also inhibited hyperactivity in olfactory bulb-removed rats. Given these results together with cumulated findings, it is suggested that CP and TP may have a novel antidepressant-like effect, and that the effect may be caused at least partly through the action on the catecholaminergic system in the brain.