



MAO A knock-out (KO), MAO A/B KO and forebrain specific MAO A knock-in transgenic mice as models for studying aggressive behavior

Kevin Chen and Jean C. Shih, Dept. Molecular Pharmacology & Toxicology, School of Pharmacy, University of Southern California, 1985 Zonal Ave, Los Angeles, CA 90089-9121

Aggressive behavior was observed in Monoamine Oxidase A knock out (KO) mice.

MAO A specific substrate serotonin, dopamine and norepinephrine were increased in brain. None of these substrates were increased in MAO B KO mice and only MAO B specific substrate phenylethylamine increased in these mice. No aggressive behavior was manifested in MAO B KO mice. Recently a hyper-reactive male mouse was identified in MAO B KO colony. A point mutation in MAO A gene was found which caused premature termination of MAO A transcription in this line of mice. The absence of MAO A enzyme activity in MAO B KO mice resulted in MAO A/B KO mice with highly increased serotonin, norepinephrine, dopamine and phenylethylamine compared with MAO A or MAO B single KO mice. The aggressive behavior can not be quantified in residence and intruder test. However, frequent fighting and numerous bite marks have been observed in male MAO A/B double KO mice when housed together. Therefore, the aggressive behavior is associated with increased brain level of MAO A specific substrate, mostly noticeable in serotonin. The excess serotonin also associated with the absence of barrelfield structure in the forebrain. This structure is formed at a critical stage before postnatal P11. Administration of tryptophan hydroxylase inhibitor para-chlorophenylalanine before P9, which blocks the biosynthesis of serotonin, rescues the abnormal structure and adult aggressive behavior. Forebrain, including amygdala, has been implicated as the critical region for aggression. This hypothesis has been tested by creating a MAO A knock-in transgenic mice in which the MAO A gene was specifically targeted to the forebrain region using CaMKIIa promoter directing the human MAO A cDNA expression. The MAO A knock-in transgenic mice in MAO A KO mice reduced the neurotransmitter levels to normal, restoring the barrelfield structure, and reduced the aggressive behavior to normal as determined by residence-intruder test.

This work was supported by NIMH grants R37 MH39085 (Merit Award), RO1 MH067968 the Boyd and Elsie Welin Professorship.