ROLE OF TRYPTOPHAN HYDROXYLASE-2 IN THE RESPONSE TO SSRI: BEHAVIORAL AND MICRODIALYSIS STUDIES IN MICE

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Despite antidepressant drugs have greatly improved the outcome of depressed patients, the delay in the response and the fact that a consistent fraction do not respond adequately still limits their efficacy. We have recently studied the role of tryptophan hydroxylase (TPH-2), a newly discovered isoform of TPH responsible for the synthesis of brain serotonin (5-HT), in the response to selective serotonin reuptake inhibitors (SSRIs) in the forced swimming test (FST), a behavioural procedure used to screen the antidepressant potential of new drugs. We found that DBA/2J and DBA/2N and BALB/c mice carrying the 1473G allele of TPH-2 have less 5-HT synthesis rate than those carrying the "C" allele such as C57BL/6J and C57BL/6N strains and did not respond to the SSRIs citalopram and paroxetine in the FST. These findings suggest that strain difference in the effect of SSRIs are likely attributable to the genotype-dependent impairment of TPH-2. This is consistent with the fact that pharmacological inhibition of 5-HT synthesis with p-chlorophenylalanine (pCPA) prevented the effect of SSRIs in the FST and caused the relapse in depressed patients in remission with SSRIs. The fact we observed no strain differences in the brain levels of the drugs and locomotor activity in response to drug treatments rule out the possibility that these factors may contribute to the different effect of SSRIs across strains.

Using the intracerebral microdialysis technique we have found that basal extracellular 5-HT in the prefrontal cortex and dorsal hippocampus of DBA/2J and BALB/c mice is lower than in C57BL/6J and C57BL/6N strains. In addition, citalopram increased extracellular 5-HT in "non-responder" less than in "responder" strains. Pre-treatment with the 5-HT1A-receptor antagonist WAY-100635 (0.3 mg/kg s.c.) had no effect by itself but strongly enhanced citalopram-induced rise of extracellular 5-HT in the PFC of DBA/2J mice and restored its ability to reduce immobility time in the FST. Also, the 5-HT precursor tryptophan (300 mg/kg i.p.) reinstated the ability of citalopram and paroxetine to reduce immobility time in DBA/2J and BALB/c mice and pCPA prevented the anti-immobility effect of paroxetine plus tryptophan combination.

The results support the importance of 5-HT transmission in the response to SSRIs and suggest that comparison of strains of mice differing for their ability to synthesize 5-HT is a useful tool to test pharmacological strategies aimed at improving the response to SSRIs.