Mouse strain differences in SSRI sensitivity correlate with serotonin transporter binding and function

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Selective serotonin reuptake inhibitors (SSRIs) bind 5-HT transporters, leading to the accumulation of 5-HT and amelioration of depression. Although different mouse strains show varying sensitivity to SSRIs in mouse models of depression, the underlying mechanism of these strain differences remains unclear. Here, the SSRI citalopram dose-dependently reduced immobility time in both the FST and TST in DBA/2J mice but not C57BL/6J mice, whereas fluoxetine showed the opposite results. Paroxetine similarly reduced immobility time in both strains. The affinity of citalopram for the 5-HT transporter was 700-fold higher in DBA/2J mice than in C57BL/6J mice, whereas the affinity of fluoxetine was 100-fold higher in C57BL/6J mice than in DBA/2J mice. Furthermore, high citalopram concentrations were required for [3H]5-HT uptake in C57BL/6J but not in DBA/2J mouse cortical synaptosomes, whereas fluoxetine showed the opposite results. The effects of paroxetine on 5-HT transporter binding and synaptosomal 5-HT uptake were similar in the two strains. These results suggest that immobility duration depends on 5-HT transporter binding levels, which lead to apparent strain differences in immobility time in the FST and TST. Furthermore, differences in 5-HT transporter binding may cause variations in SSRI effects on behaviors.