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Acute and Chronic Effects of Citalopram on 5-HT_{1A} Receptor—Labeling by [^{18}F]MPPF and—Coupling to Receptors-G Proteins

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ABSTRACT Selective serotonin reuptake inhibitors take several weeks to produce their maximal therapeutic antidepressant effect. This delay has been attributed to the gradual desensitization of somatodendritic serotonin 5-HT_{1A} autoreceptors. We evaluated adaptive changes of 5-HT_{1A} receptors after acute and chronic citalopram challenges in rat. Small animal positron emission tomography trial and quantitative ex vivo autoradiography studies using [^{18}F]MPPF were employed, as well as in vitro 8-OH-DPAT-stimulated [^{35}S]-GTPγS binding assay. Additionally, 5-HT_{1A} receptor knock-out mice were used to assess the specificity of [^{18}F]MPPF. Acute treatment with citalopram did not alter [^{18}F]MPPF binding in dorsal raphe nucleus (DR), frontal cortex, or hippocampus. The absence of [^{18}F]MPPF binding in the brain of 5-HT_{1A} knock-out mice demonstrates the specificity of MPPF for 5-HT_{1A} receptor brain imaging, but the high affinity of [^{18}F]MPPF compared to 5-HT suggests that it would only be displaced by dramatic increases in extracellular 5-HT. Chronic citalopram did not modify 5-HT_{1A} receptor density in any of the brain regions studied. In addition, this treatment did not modify 8-OH-DPAT-stimulated [^{35}S]-GTPγS binding in DR, although a significant increase was observed in frontal cortex and hippocampus. [^{18}F]MPPF appears to be an efficient radioligand to quantify specifically 5-HT_{1A} receptor density in brain imaging. The delayed therapeutic efficacy of citalopram did not appear to be linked to either a downregulation of 5-HT_{1A} receptors or to a 5-HT_{1A} receptor-G protein decoupling process in serotonergic neurons, but to increased functional sensitivity of postsynaptic 5-HT_{1A} receptors. **Synapse 63:106–116, 2009.**