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]-GTP$_{\gamma}$S 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]-GTP$_{\gamma}$S 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. © 2008 Wiley-Liss, Inc.

INTRODUCTION

Dysregulation of brain 5-HT neurotransmission has been shown to be intricately associated with complex psychiatric disorders, such as depression and anxiety disorders (Cryan and Leonard, 2000; Jones and Blackburn, 2002; Kiss, 2008; Law et al., 2007). Among the diverse 5-HT receptor subtypes known to date, interactions with metabotropic 5-HT$_{1A}$ receptors seem to be most relevant for understanding the mechanisms of action of antidepressants, anxiolytics such as azapir-