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Lu AA21004, a novel multimodal antidepressant, produces regionally selective increases of multiple neurotransmitters--a rat microdialysis and electrophysiology study.

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Abstract

The monoaminergic network, including serotonin (5-HT), norepinephrine (NE), and dopamine (DA) pathways, is highly interconnected and has a well-established role in mood disorders. Preclinical research suggests that 5-HT receptor subtypes, including 5-HT1A, 5-HT1B, 5-HT3, and 5-HT7 receptors as well as the 5-HT transporter (SERT), may have important roles in treating depression. This study evaluated the neuropharmacological profile of Lu AA21004, a novel multimodal antidepressant combining 5-HT3 and 5-HT7 receptor antagonism, 5-HT1B receptor partial agonism, 5-HT1A receptor agonism, and SERT inhibition in recombinant cell lines. Extracellular 5-HT, NE and DA levels were evaluated in the ventral hippocampus (vHC), medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) after acute and subchronic treatment with Lu AA21004 or escitalopram. The acute effects of LuAA21004 on NE and DA neuronal firing were also evaluated in the locus coeruleus (LC) and ventral tegmental area (VTA), respectively. Acute Lu AA21004 dose-dependently increased 5-HT in the vHC, mPFC and NAc. Maximal 5-HT levels in the vHC were higher than those in the mPFC. Furthermore, mPFC 5-HT levels were increased at low SERT occupancy levels. In the vHC and mPFC, but not the NAc, high Lu AA21004 doses increased NE and DA levels. Lu AA21004 slightly decreased LC NE neuronal firing and had no effect on VTA DA firing. Results are discussed in context of occupancy at 5-HT3, 5-HT1B and 5-HT1A receptors and SERT. In conclusion, Lu AA21004, acting via two pharmacological modalities, 5-HT receptor modulation and SERT inhibition, results in a brain region-dependent increase of multiple neurotransmitter concentrations.

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