The adventures of a bioanalytical chemist in the never-never land of antidepressants: Using metabolomics to find a solution to the “ketamine paradigm”

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(R,S)-Ketamine is a chiral phencyclidine derivative that produces rapid and short-lived anesthesia via inhibition of the N-methyl-d-aspartate (NMDA) receptor. The anesthetic activity of this drug has been associated with the parent compound and to a lesser degree with the N-demethylated metabolite (R,S)-norketamine, while other (R,S)-ketamine metabolites were designated as “inactive”, the “Ketamine Paradigm”. Recent studies demonstrated that a single sub-anesthetic dose of (R,S)-ketamine produces rapid and profound antidepressant response. As part of our studies of this effect in patients with treatment-resistant depression and bipolar depression, we developed a stereoselective lc/ms/ms assay capable of quantifying all of the major (R,S)-ketamine metabolites. The analysis of plasma samples demonstrated that (R,S)-ketamine was rapidly and extensively transformed into multiple metabolites including (2S,6S;2R,6R)-hydroxynorketamine and that these metabolites were associated with antidepressant response. Using mouse models of depression we were able to confirm these findings and to demonstrate that (2R,6R)-hydroxynorketamine and (2S,6S)-hydroxynorketamine produced profound antidepressant responses. Data from a metabolomic study of plasma samples obtained from patients with bipolar depression treated with (R,S)-ketamine indicated that changes in mitochondrial activity was associated with therapeutic response. Cell-based studies of changes in mitochondrial metabolome produced by (2R,6R)-hydroxynorketamine, (2S,6S)-hydroxynorketamine, (R)-ketamine and (S)-ketamine have indentified cellular pathways associated with antidepressant response and confirmed that (2R,6R)-hydroxynorketamine is a potent antidepressant agent. This talk will address how our ability to accurately measure chemical and biological changes led us to a new “Ketamine Paradigm” and to the identification of the ketamine metabolites responsible for the drug’s antidepressant activity. The presentation will also discuss the development of a pharmacophore model that is being used to design a new family of antidepressant drugs.