The adventures of a bioanalytical chemist in the never-never land of antidepressants: Using metabolomcs 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 in to multiple metabolites including (2*S*,6*S*;2*R*,6*R*)-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 (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-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 (2*R*,6*R*)-hydroxynorketamine, (2*S*,6*S*)-hydroxynorketamine, (*R*)-ketamine and (*S*)-ketamine have indentified cellular pathways associated with antidepressant response and confirmed that (2*R*,6*R*)-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.