Depression is among the leading causes of death and disability worldwide. Despite decades of research, the antidepressant therapies available to patients are still unable to help all those who suffer from depression. Indeed, treatment resistant depression (TRD) affects as many as one third of all patients. In search of a solution, researchers are exploring animal models that are more similar to TRD in humans, and developing and testing new theories of the pathogenesis of depression – i.e. theories explaining the underlying biological chain of events that cause it.

For a long time it was believed that changes in monoamine neurotransmitters – dopamine, serotonin, noradrenaline – are mostly responsible for depression. It is now increasingly understood that those systems, while indeed very important in controlling emotions, mood, responses to stress, motivation and other aspects affected by this disease, are in themselves shaped by neuronal plasticity. Plasticity is the process by which neurons themselves, as well as synapses that connect these neurons, grow and change over time. Plasticity predominantly involves glutamate and GABA – two main neurotransmitters that govern excitation and inhibition, respectively, of neuronal cells. We now believe that it is the disturbance of those plasticity processes that is responsible for changes in the brain that give rise to depression. Plasticity can be affected by shifting balance between excitation and inhibition, prolonged stress hormone signaling, or a decrease in signals and molecular mechanisms that normally promote growth (neurotrophic factors).

The purpose of our project is to study the properties and plasticity of both excitatory and inhibitory inputs into dorsal raphe (DRN) – the primary area of the brain that produces and releases serotonin. We will focus on two such structures, which are known to connect to the DRN: the prefrontal cortex and the lateral habenula. To this end, we will use Wistar-Kyoto (WKY) rats, a strain of animals in which researchers have found spontaneous, innate depression-like behavior (anxiety, vulnerability to stress, lack of drive and motivation as well as anhedonia – weakened responsiveness to rewarding stimuli). An even more important feature of WKY rats is that they exhibit properties similar to TRD in that they do not respond normally to most classical antidepressants, but *do* indeed respond to some therapies like transcranial stimulation or ketamine (which is now considered as a fast-acting antidepressant drug) which are still effective in some persons with TRD.

In the course of our work, we will use electrophysiological methods, such as patch-clamp recordings, in combination with imaging and molecular methods, to characterize neurons in the DRN, cortex and habenula of WKY rats. We will then use special viral vectors that allow for precise retrograde – “backtracking” – staining of only those neurons in the cortex and habenula that send their connections into the DRN. This will allow us to assess whether the properties and plasticity of those specific neurons are different from other (non-DRN projecting) neurons of this type, and also whether any of those properties differ in WKY rats in comparison to control, “non-depressed” rats. We will then administer ketamine to these animals and see whether any of these populations of neurons are specifically affected. And finally, with the aid of special genetically encoded tools – chemogenetics and optogenetics – we will manipulate these specific circuits directly, to determine whether a specific neural pathway between the cortex, the habenula and the DRN is responsible for ketamine’s antidepressant effects.

The proposed studies will allow us to identify how mechanisms upstream of the serotonin system can alter its function in depression and how plasticity of those connections works in anatomically precisely defined circuits, potentially helping identify new and better defined targets for novel therapies that TRD patients urgently need.