ABSTRACT

There is a major unmet need for the treatment of depression because current pharmacotherapies for depression require prolonged administration for clinical improvement and they are associated with high non-response rate. In contrast, recent evidence has shown that allopregnanolone, a neuroactive steroid, exerts rapid and sustained antidepressant effects. However, a circuit and synaptic dissection of the mechanisms underpinning allopregnanolone’s antidepressant effects is lacking. Without such knowledge our capability to harness the properties of allopregnanolone for the rational design of more targeted treatments will be limited. Accordingly, the goal of this proposal is to identify circuits and synaptic determinants responsible for allopregnanolone’s ability to ameliorate a core domain of depression, anhedonia. Anhedonia -defined as diminished pleasure from, or interest in, previously rewarding activities- is commonly precipitated by exposure to chronic stress and it is well suited to study in laboratory animals.

Specifically, in preliminary studies, we found that chronic stress induces hedonic deficits in mice and reduces excitatory transmission within the Nucleus Accumbens (NAc), a brain region with crucial roles in hedonic drive. In contrast, an acute systemic administration of allopregnanolone reverses both phenomena. Moreover, allopregnanolone acutely activates a specific input projecting to the NAc, the medial prefrontal cortex (mPFC). Here, we will first identify whether allopregnanolone exerts its anti-anhedonic effects by changing synaptic efficacy within genetically specified populations of neurons within the NAc (aim 1). Then, we are going to examine whether such synaptic modifications and anti-anhedonic effects are driven by the mPFC input to the NAc (aim 2).