Huntington’s disease (HD) is a heritable neurodegenerative disorder characterized by cognitive and behavioral dysfunctions (motor impairments) and striatal neurodegeneration in later stages. HD is caused by an expansion of glutamine codons in the glutamic acid decarboxylase (GAD) gene, resulting in overproduction of GABA. Overproduction of GABA may lead to neuronal death due to increased glutamatergic neurotransmission. GABA neurotransmission may lead to the neurochemical changes seen in HD. In excess, GABA can promote excitotoxicity in the brain, leading to neuronal cell death and, in deficit, in glutamatergic neurons by reducing excitatory neurotransmission. HD-caused cell death observed in transgenic HD mice involves increased excitatory amino acid (EAA) sensitivity (NMDA receptors, NMDAs) and decreased sensitivity to antagonists (<br>Fig. 1B). These EAA-mediated excitations contribute to neurodegeneration and are likely the cause of the movement impairments that are characteristic of HD in later stages. There is some evidence for the role of glutamatergic transmission in the pathogenesis of HD, specifically reduced baseline GABA levels have been found to have a neuroprotective effect in vivo (Fig. 2). Additionally, the expression of anti-apoptotic genes in HD animal models has been linked to the levels of GABA (Fig. 2C).<br>Recent findings have shown that the striatum is a key brain region affected in HD, with an increased GABAergic tone and decreased glutamatergic transmission. This suggests that reducing glutamatergic transmission and increasing GABAergic transmission may be beneficial in treating HD. One way to achieve this is through the use of GABAergic agonists, such as GABA, which has been shown to have neuroprotective effects in HD models. However, the use of GABA as a drug is limited due to its short half-life and rapid clearance from the brain. One approach to overcoming these limitations is the use of microdialysis, a technique that allows for the continuous monitoring of neurotransmitter levels in the brain. In this study, we used microdialysis to measure the effects of GLYX-13, a GABAergic agonist, on the extracellular levels of GABA, glutamate, and glutamine in the striatum of HD mouse models. The results showed a significant decrease in glutamate levels and an increase in GABA levels in the striatum of HD mouse models treated with GLYX-13. This suggests that GLYX-13 is effective in reducing glutamatergic transmission and increasing GABAergic transmission, which may have therapeutic potential for HD. In conclusion, the use of GLYX-13 as a GABAergic agonist in HD models shows promise in reducing glutamatergic transmission and increasing GABAergic transmission, which may have therapeutic potential for HD. Further studies are needed to fully understand the mechanism of action and the long-term effects of GLYX-13 in HD models.