Major depression is a common psychiatric disorder that affects over 120 million people worldwide, with a lifetime prevalence of 10% to 15%. Our previous study indicates that deficiency of astrocyte-derived ATP in the medial prefrontal cortex (mPFC) modulates depressive-like behaviors. However, the molecular mechanisms are not fully understood. Astrocytes release gliotransmitters to modulate synaptic activity, and abnormal activation of neuronal circuits involved in mood modulation may give rise to psychiatric disorders. Thus, we explore whether astrocytes modulate depressive-like behaviors through regulating synaptic activity. We found that GABAergic, but not glutamatergic synaptic activity was impaired in the mPFC of depressed mice due to a presynaptic mechanism. ATP could reverse the reduced inhibitory synaptic activity. IP3R2 knockout mice, in which ATP release in astrocytes was specifically diminished, displayed depressive-like behaviors and a similar impairment in synaptic transmission as depressed mice and the reduced GABAergic synaptic activity was also rescued by ATP. ATP modulation of GABAergic transmission and depressive-like behaviors was mediated by P2X2 receptors. Moreover, a reduced GABAergic input was observed in LHb-projecting mPFC pyramidal neurons in the depressed mice, suggesting an over-activation of mPFC-LHb circuit. The above data indicate that astrocyte-derived ATP may modulate depressive-like behaviors through GABAergic inhibition in the mPFC. Interestingly, we found that the ratio of ADP/ATP but not ATP itself in the VTA may be a key player in the pathogenesis of depression.