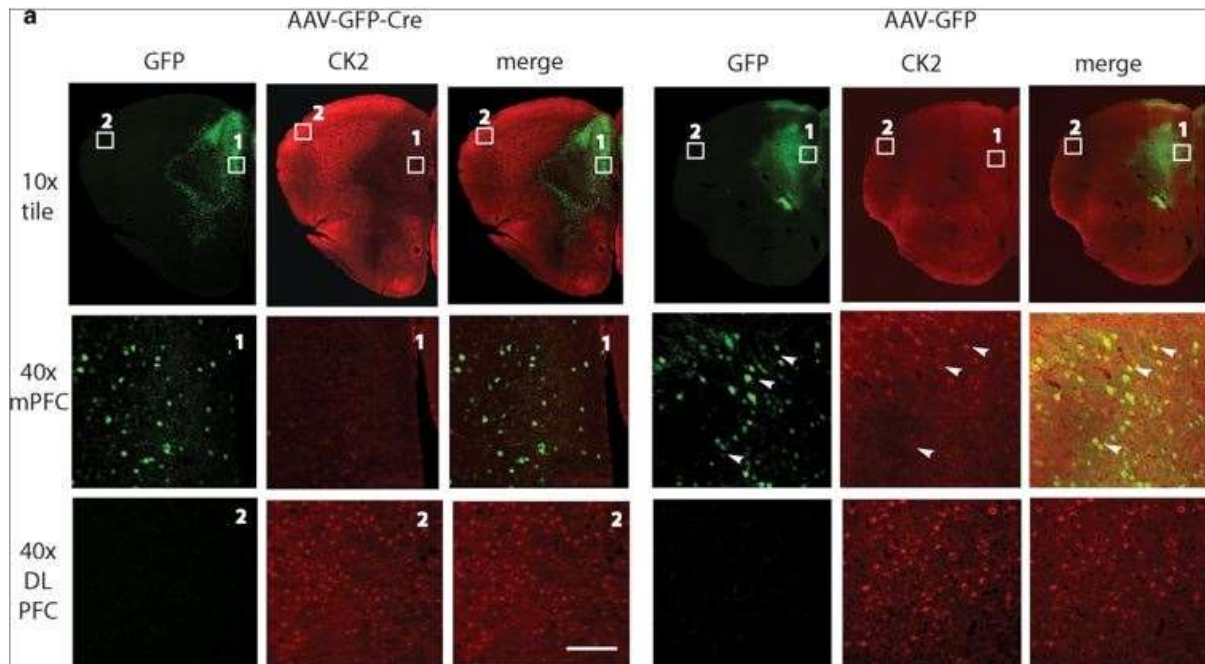


Castello J, LeFrancois B, Flajolet M, Greengard P, Friedman E, Rebholz H. [CK2 regulates 5-HT4 receptor signaling and modulates depressive-like behavior](#). *Mol Psychiatry*. 2018 Apr;23(4):872-882. doi: 10.1038/mp.2017.240. Epub 2017 Nov 21. PubMed PMID: 29158580.



The serotonergic neurotransmitter system has been widely implicated in the pathophysiology of mood-related disorders such as anxiety and major depressive disorder (MDD). The onset of therapeutic efficacy of traditional antidepressants is delayed by several weeks. The 5-HT4 receptor has emerged as a new therapeutic target since agonists of this receptor induce rapid antidepressant-like responses in rodents. Here we show that the 5-HT4 receptor is regulated by CK2, at transcriptional and post-transcriptional levels. We present evidence, in two different CK2 α knockout mouse lines, that this regulation is region-specific, with the 5-HT4 receptor upregulated in prefrontal cortex (PFC) but not striatum or hippocampus where CK2 α is also ablated. 5-HT4 receptor signaling is enhanced in vitro, as evidenced by enhanced cAMP production or receptor plasma membrane localization in the presence of CK2 inhibitor or shRNA targeting CK2 α . In vivo, 5-HT4 receptor signaling is also upregulated since ERK activation is elevated and sensitive to the inverse agonist, GR113808 in the PFC of CK2 α KO mice. Behaviorally, KO mice as well as mice with AAV-mediated deletion of CK2 α in the PFC show a robust 'anti-depressed-like' phenotype and display an enhanced response to antidepressant treatment when tested in paradigms for mood and anxiety. Importantly, it is sufficient to overexpress the 5-HT4 receptor in the mPFC to generate mice with a similar 'anti-depressed-like' phenotype. Our findings identify the mPFC as the region that mediates the effect of enhanced 5-HT4 receptor activity and CK2 as modulator of 5-HT4 receptor levels in this brain region that regulates mood-related phenotypes.