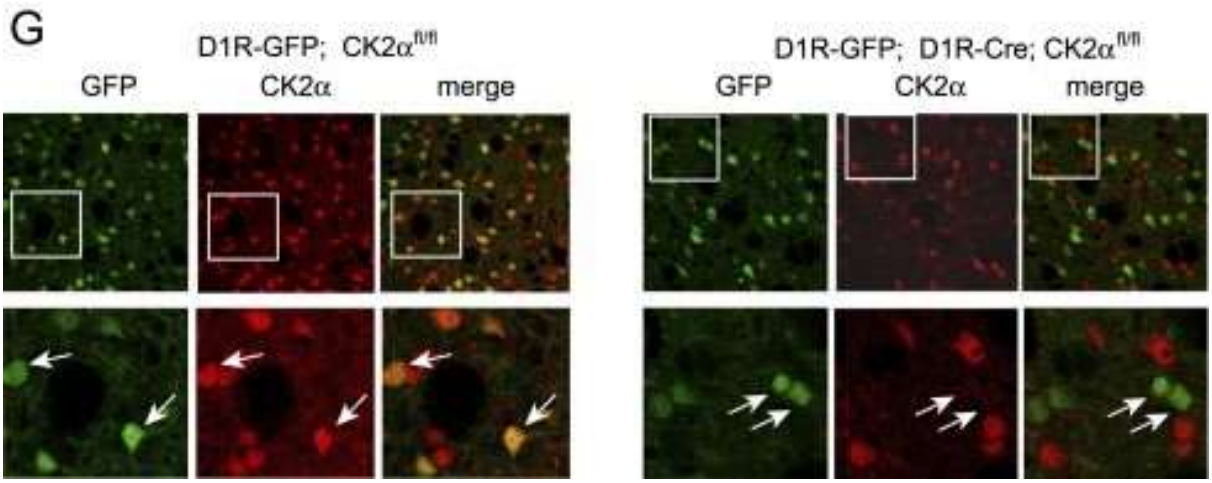
Rebholz et al. 2013. Biol Psychiatry

Rebholz H, Zhou M, Nairn AC, Greengard P, Flajolet M. Selective knockout of the casein kinase 2 in d1 medium spiny neurons controls dopaminergic function. Biol Psychiatry. 2013 Jul 15;74(2):113-21. doi: 10.1016/j.biopsych.2012.11.013. Epub 2013 Jan 3. PubMed PMID: 23290496; PubMed Central PMCID: PMC3878430.



BACKGROUND:

Dopamine, crucial for the regulation of motor function and reward, acts through receptors mainly expressed in striatum as well as cortex. Dysregulation of dopaminergic signaling is associated with various neuropsychiatric disorders. Consequently, dopamine-regulating drugs are effectively used in treating these disorders, such as L-DOPA for Parkinson's disease, methylphenidate for attention-deficit/hyperactivity disorder, or antipsychotics for schizophrenia. As a result, there has been much interest in dissecting signaling networks in the two morphologically indistinguishable D1- and D2-receptor-expressing medium spiny neurons. Our previous results highlighted a role for casein kinase 2 (CK2) in the modulation of dopamine D1 receptor (D1R) signaling in cells.

METHODS:
To study the importance of CK2 in vivo, we have selectively knocked out CK2, in either D1- or D2-medium spiny neurons (MSNs) and characterized the mice behaviorally and biochemically (n = 4-18).

RESULTS:
The D1-MSN knockout mice exhibited distinct behavioral phenotypes including novelty-induced hyperlocomotion and exploratory behavior, defective motor control, and motor learning. All of these behavioral traits are indicative of dysregulated dopamine signaling and the underlying mechanism appears to be an alteration of D1R signaling. In support of this hypothesis, D1R levels were upregulated in the knockout mice, as well as phosphorylation of DARPP-32 (dopamine- and cyclic adenosine monophosphate [cAMP]-regulated phospho-protein of 32 kDa), most of the behavioral phenotypes were abolished by the D1R antagonist, SCH23390, and the D2-MSN knockout mice displayed no obvious behavioral phenotype.

CONCLUSIONS:
A single kinase, CK2, in D1-MSNs significantly alters dopamine signaling, a finding that could have therapeutic implications for disorders characterized by dopamine imbalance such as Parkinson's disease, attention-deficit/hyperactivity disorder, and schizophrenia.