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Diversity of Reporter Expression Patterns in Transgenic Mouse Lines Targeting Corticotropin Releasing Hormone-Expressing Neurons

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Background: Transgenic rodent models enabling gene-based access to specific cell populations provide potent tools for neuroscience research. The use of Cre-driver lines in combination with Cre-dependent methods for the regulation of gene expression, visualization of reporters or optogenetic activation / inhibition has yielded a large body of innovative discoveries in brain connectivity and in the contributions of specific neuronal populations–and of molecules produced in specific regions–to crucial brain functions including feeding, reward and addiction, memory and depression. Mouse lines targeting corticotropin-releasing factor (CRF/CRH) has been extensively employed to study stress neurobiology and are poised to revolutionize our understanding of the localization and connectivity of CRH-expressing neurons, and the crucial roles of CRH in normal and pathological conditions. Accurate interpretation of all studies using cell type-specific transgenic mice vitally depends on congruence between expression of the endogenous molecule and reporter: If reporter expression does not faithfully reproduce native gene expression, then effects of manipulating unintentionally-targeted cells may be misattributed.

Methods: Here, we studied CRH and reporter expression patterns in three adult transgenic mice: Crh-IRES-Cre;Ai14 (tdTomato mouse); Crfp3.0CreGFP, and Crh-GFP BAC. As gold standard, we employed the CRH antiserum generated by Vale, validating its specificity using CRH-null mice. We focused the analyses on stress-salient regions including hypothalamus, amygdala, bed nucleus of the stria terminalis (BNST) and hippocampus.

Results: Expression patterns of endogenous CRH were consistent among wild-type (WT) and transgenic mice. In tdTomato mice, most CRH-expressing neurons co-expressed the reporter, yet the reporter identified a few non-CRH-expressing pyramidal-like cells in hippocampal CA3. In Crfp3.0CreGFP mice, co-expression of CRH and the reporter was found in central amygdala and, less commonly, in other evaluated regions. In Crh-GFP BAC mice, the large majority of neurons expressed either CRH or reporter, with little overlap.

Conclusions: These data highlight significant diversity in concordant expression of reporter and endogenous CRH among three available transgenic mice. These findings should be instrumental in interpreting important scientific findings emerging from the use of these potent neurobiological tools.

Keywords: Animal Models, transgenic mice, optogenetics, Corticotropin-Releasing Hormone, stress

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