www.elsevier.com/locate/developmentalbiology

Canonical Wnt signaling regulates patterning, differentiation and nucleogenesis in mouse hypothalamus and prethalamus

Elizabeth A. Newman, Dan Wu, Makoto Mark Taketo, Jiangyang Zhang, Seth Blackshaw

PII: S0012-1606(18)30451-2
DOI: https://doi.org/10.1016/j.ydbio.2018.07.021
Reference: YDBIO7825

To appear in: *Developmental Biology*

Received date: 25 June 2018
Revised date: 26 July 2018
Accepted date: 26 July 2018

Cite this article as: Elizabeth A. Newman, Dan Wu, Makoto Mark Taketo, Jiangyang Zhang and Seth Blackshaw, Canonical Wnt signaling regulates patterning, differentiation and nucleogenesis in mouse hypothalamus and prethalamus, *Developmental Biology,* https://doi.org/10.1016/j.ydbio.2018.07.021

Canonical Wnt signaling regulates patterning, differentiation and nucleogenesis in mouse hypothalamus and prethalamus.

Elizabeth A. Newman[1], Dan Wu[2], Makoto Mark Taketo[7], Jiangyang Zhang[8], and Seth Blackshaw[1,3-6].

[1]Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[2]Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[3]Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[4]Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[5]Center for Human Systems Biology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[6]Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, MD, USA;
[7]Division of Experimental Therapeutics, Graduate School of Medicine, Kyoto University, Kyoto, Japan;
[8]Department of Radiology, NYU Langone School of Medicine, New York, NY.

*Corresponding author: sblack@jhmi.edu (S.B.)

Abstract:

The hypothalamus is a small, but anatomically and functionally complex, region of the brain whose development is poorly understood. In this study, we have explored its development by studying the canonical Wnt signalling pathway, generating gain and loss of function mutations of beta-catenin (*Ctnnb1*) in both hypothalamic and prethalamic neuroepithelium. Deletion of *Ctnnb1* resulted in an anteriorized and hypoplastic hypothalamus. Posterior structures were lost or reduced, and anterior structures were expanded. In contrast, overexpression of a constitutively active mutant form of *Ctnnb1* resulted in severe hyperplasia of prethalamus and hypothalamus, and expanded expression of a subset of posterior and premamillary hypothalamic markers. Moderate defects in differentiation of *Arx*-positive GABAergic neural precursors were observed in both prethalamus and hypothalamus of *Ctnnb1* loss of function mutants, while in gain of function mutants, their differentiation was completely suppressed, although markers of prethalamic progenitors were preserved. Multiple other region-specific markers, including several specific posterior hypothalamic structures, were also suppressed in *Ctnnb1* gain of function mutations. Severe, region-specific defects in hypothalamic nucleogenesis were also observed in both gain and loss of function mutations of *Ctnnb1*. Finally, both gain and loss of function of *Ctnnb1* also produced severe, cell non-autonomous disruptions of pituitary development. These findings demonstrate a central and multifaceted role for canonical Wnt signalling in regulating growth, patterning, differentiation and nucleogenesis in multiple diencephalic regions.