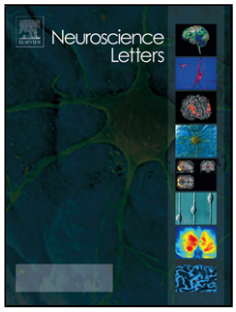

Title: The posterior pituitary expresses the serotonin receptor 2C

Authors: Justin R. Welden, Zhaiyi Zhang, Marilyn J. Duncan, Marina Falaleeva, Timothy Wells, Stefan Stamm

PII: S0304-3940(18)30454-3
DOI: https://doi.org/10.1016/j.neulet.2018.06.051
Reference: NSL 33682

To appear in: *Neuroscience Letters*

Received date: 3-4-2018
Revised date: 19-6-2018
Accepted date: 27-6-2018

Please cite this article as: Welden JR, Zhang Z, Duncan MJ, Falaleeva M, Wells T, Stamm S, The posterior pituitary expresses the serotonin receptor 2C, *Neuroscience Letters* (2018), https://doi.org/10.1016/j.neulet.2018.06.051

The posterior pituitary expresses the serotonin receptor 2C

Justin R. Welden[1], Zhaiyi Zhang[1], Marilyn J. Duncan[2], Marina Falaleeva[1], Timothy Wells[3] and Stefan Stamm[1]*

[1]Molecular and Cellular Biochemistry, University of Kentucky College of Medicine, Lexington, KY 40503
[2]Dept. of Neuroscience, University of Kentucky College of Medicine, Lexington, KY 40536
[3]School of Biosciences, Cardiff University, Cardiff, CF10 3AX, United Kingdom

*corresponding author Stefan@stamms-lab.net

Highlights

- The two splice variants of the serotonin receptor 2C are expressed in posterior pituitary and pituitary stalk
- The ratio of the splice variants in pituitary is changed in a mouse model of Prader-Willi syndrome
- Systemic injection of a splice-site changing oligonucleotide changes the ratio of the splicing isoforms

Abstract

The serotonin receptor 2C (5HT2C) is an important drug target to treat obesity and depression. Its pre-mRNA undergoes alternative splicing, encoding a short RNA1 isoform that is localized intracellularly and a full-length isoform (RNA2) that can reach the cell membrane. These splicing isoforms are deregulated in Prader-Willi syndrome (PWS), due to the loss of a trans-acting regulatory RNA, SNORD115. Here we show that the 5HT2C mRNA is expressed in the posterior pituitary, suggesting that 5HT2C mRNA is generated in the hypothalamus and subsequently conveyed by axonal transport. In the pituitary, the ratio of 5HT2C isoforms is regulated by feeding, and can be manipulated using a splice-site changing oligonucleotide injected into the blood. The pituitary expression of the 5HT2C mRNA may constitute a previously unknown mechanism whereby serotonin in the circulation or drugs targeting the 5HT2C might induce side-effects. Finally, the deregulation of 5HT2C splicing isoforms in PWS could contribute to the known hormonal imbalances.

Keywords: serotonin receptor 2C, pituitary, alternative splicing, Prader-Willi syndrome

1. Introduction

1.1. The serotonin receptor is targeted by a large number of drugs

The serotonin receptor 2C (5HT2C) is a seven transmembrane receptor regulating mood and appetite through its actions in the central nervous system [21, 42]. Its deregulation is involved in depression [30], suicidal behavior [11],