MEDWIN PUBLISHERS
Committed to create value for Researchers

Diabetes and Obesity International Journal
ISSN: 2574-7770

Ciliary Adenylyl Cyclase3: A New Player in Obesity

Cao H[1] and Storm DR[2]*

[1]Institutes of Brain Science and State Key Laboratory of Medical Neurobiology, Fudan University, China

[2]Department of Pharmacology, School of Medicine, University of Washington, USA

Mini Review

Volume 2 Issue 2

Received Date: February 21, 2017

Published Date: March 10, 2017

DOI: 10.23880/doij-16000151

***Corresponding author:** Daniel R Storm, Department of Pharmacology, School of Medicine, University of Washington, Seattle, Washington 98195, USA, Email: dstorm@uw.edu

Abstract

Recent studies with transgenic mice and human genetic studies have implicated defects in the expression of type 3 adenylyl cyclase (AC3) in obesity. Human genetic studies have indicated that AC3 polymorphisms are associated with body mass index (BMI) in the populations with obesity and type 2 diabetes. Our studies using both AC3 global knockout mice and AC3 conditioned knockout mice demonstrated that AC3 plays an important role in the regulation of body weight, implying that AC3 might be a potential drug target site to combat obesity. We propose that AC3 in the hypothalamus plays an important role in leptin signaling.

Keywords: AC3; Obesity; Cilia

Abbreviations: AC: Adenylyl Cyclase; BMI: Body Mass Index; cAMP-3',5': Cyclic Adenosine Monophosphate; GPCRs: G-Protein Coupled Receptors; GWAS: Genome-Wide Association Studies; SNP: Single Nucleotide Polymorphisms

Introduction

Obesity is a major health issue associated with complications that cause significant morbidity and mortality. During 2009-2010, the prevalence of obesity in the United States was about 36% among adult men, 36% among adult women, and 17% among children and adolescents [1]. It will increase to 60% in adult men, 40% in adult women and 25% in children by 2050 according to current trends. Obese individuals have a higher risk for a number of diseases including type 2 diabetes, cardiovascular disease, metabolic syndrome, hypertension, certain forms of cancer, and sleep-breathing disorders [2]. Furthermore, obesity decreases longevity and lowers the general quality of life [3-6]. Although intensive effort has been devoted to anti-obesity therapy, the percentage of obese individuals continues to increase globally in both developed and developing counties.

Obesity is a disorder characterized by excessive, abnormal fat accumulation as a result of increased intake and decreased physical activity. However, mounting evidence from animal models, monogenic obesity in humans, twin and adoption studies, and genome-wide association studies (GWAS) has suggested that genetic factors affect the risk of developing obesity [7-9]. One of them is the ADCY3 gene, which encodes a member of the adenylyl cyclase (AC) family of proteins.

Adenylyl cyclases (ACs) catalyze the synthesis of cyclic 3'5'-AMP (cAMP) from ATP. There are ten AC isoforms that have been cloned and characterized in mammals [10]. AC3 is special among the membrane-associated ACs due to its predominant expression in cilia [11]. It has been reported that AC3 gene polymorphisms are associated with obesity in a group of Swedish men and also in the Han Chinese population [7,12]. In another study, a genome-wide association analysis based on height-adjusted BMI found that SNPs in AC3 were associated at genome-wide significance

level (rs11676272 (0.28 kg/m3.1 change per allele G (0.19, 0.38), P56 3 1029). The association of AC3 with obesity is apparently driven by a miss-sense variant [8]. These human genetic studies suggested that AC3 might play an important role in the regulation of body weight.

In order to further evaluate the genetic role of AC3 in obesity, we generated a mouse model of AC3 deficiency. We monitored the weight of $AC3^{-/-}$ mice, over an extended period of time [9]. Although $AC3^{-/-}$ mice are about half the size of their wild type littermates right after birth, they achieve normal size and weight after two months. As the mice age, however, they become obese and are significantly heavier than wild type littermates. Adult male $AC3^{-/-}$ mice are about 40% heavier than wild type male mice, while female $AC3^{-/-}$ mice are 70% heavier. The gain in weight is due to increased fat mass and larger adipocytes. Before the onset of obesity, young $AC3^{-/-}$ mice (2 months) exhibit reduced physical activity, increased food consumption, and leptin insensitivity. On the other hand, a gain-of-function mutation of AC3 protects mice from diet-induced obesity providing further evidence that AC3 may play a major role in weight control [13]. Interestingly, AC3 is not expressed in white adipose and AC3 mice exhibit normal lipolysis.

AC3 is widely expressed in primary cilia throughout the nervous system [11]. $AC3^{-/-}$ mice exhibit a number of other phenotypes including anosmia, depression, and defects in extinction of hippocampus dependent memory that confound interpretation of the obesity phenotype in the global AC3 knockout [14-16]. Therefore, we made a floxed AC3 mouse strain so that we can ablate AC3 in specific brain regions directly or indirectly implicated in obesity [14,17]. Several different sites within the hypothalamus are known to be important in regulating body weight including the ventromedial hypothalamic nucleus (VMH).

To further explore whether obesity in $AC3^{-/-}$ mice is due to lose of AC3 in the hypothalamus, we selectively disrupted AC3 expression in the ventral medial hypothalamus (VMH) by sterotaxically injection of AAV1-CRE-GFP into the hypothalamus. Our data suggest $AC3^{flox/flox}$ mice became obese after the administration of AAV-CRE into the hypothalamus. Both male and female AC3 floxed mice showed heavier body weight than control mice. Furthermore, mice with selective ablation of AC3 expression in the ventromedial hypothalamus also showed increased body weight and food consumption. Apparently ciliary AC3 signaling cross talks with the leptin-mediated signaling pathway in the hypothalamus.

Taken together, these data strongly imply an important role of AC3 in the regulation of body weight. Since $AC3^{-/-}$ knockout mice also exhibit depression, isolation of drugs that activate AC3 may be of considerable therapeutic importance.

Acknowledgement

This work was supported by National Natural Science Fund of China (NSFC 31371123) and by National Institutes of Health Grant DC04156. None of the authors received any financial or monetary transfer of value for their participation in the writing of the manuscript from any of the pharmaceutical company so far.

Conflicts of Interest

The authors have contributed independently to express their personal views in this paper and there is no conflict of interest.

References

1. Narayanaswami V, Dwoskin LP (2017) Obesity: Current and potential pharmacotherapeutics and targets. Pharmacology & Therapeutics 170: 116-147.

2. Kopelman PG (2000) Obesity as a medical problem. Nature 404(6778): 635-643.

3. Bray GA (2006) Obesity: The disease. J Med Chem 49: 4001-4007.

4. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB (2003) Years of life lost due to obesity. JAMA 289(20: 187-193.

5. Spiegelman BM, Flier JS (2001) Obesity and the regulation of energy balance. Cell 104(4): 531-543.

6. Fontaine KR, Barofsky I (2001) Obesity and health-related quality of life. Obes Rev 2(3): 173-182.

7. Nordman S, Abulaiti A, Hilding A, Långberg EC, Humphreys K, et al. (2008) Genetic variation of the adenylyl cyclase 3 (AC3) locus and its influence on type 2 diabetes and obesity susceptibility in Swedish men. Int J Obes (Lond) 32(3): 407-412.

8. Stergiakouli E, Gaillard R, Tavaré JM, Balthasar N, Loos RJ, et al. (2014) Genome-wide association study of height-adjusted BMI in childhood identifies functional variant in ADCY3. Obesity 22(10): 2252-2259.

9. Wang Z, Li V, Chan GC, Phan T, Nudelman AS, et al. (2009) Adult type 3 adenylyl cyclase-deficient mice are obese. PLoS One 4(9): e6979.

10. Hanoune J, Defer N (2000) Regulation and role of adenylyl cyclase isoforms. Annu Rev Pharmacol Toxicol 41: 145-147.

11. Bishop GA, Berbari NF, Lewis J, Mykytyn K (2007) Type III adenylyl cyclase localizes to primary cilia throughout the adult mouse brain. J Comp Neurol 505(5): 562-571.

12. Wang H, Wu M, Zhu W, Shen J, Shi X, et al. (2010) Evaluation of the association between the AC3 genetic polymorphisms and obesity in a Chinese Han Population. Plos one 5(11): e13851.

13. Pitman JL, Wheeler MC, Lloyd DJ, Walker JR, Glynne RJ, et al. (2014) A gain-of-function mutation in adenylate cyclase 3 protects mice from diet-induced obesity. PLos One 9: e110226.

14. Chen X, Luo J, Leng Y, Yang Y, Zweifel LS, et al. (2016) Ablation of type III adenylyl cyclase in mice causes reduced neuronal activity, altered sleep pattern, and depression-like phenotypes. Biological Psychiatry 80(11): 836-848.

15. Wang Z, Storm DR (2010) Maternal behavior is impaired in female mice lacking type 3 adenylyl cyclase. Neuropsychopharmacology 36(4): 772-781.

16. Wang Z, Phan T, Storm DR (2011) The type 3 adenylyl cyclase is required for novel object learning and extinction of contextual memory: role of cAMP signaling in primary cilia. J Neurosci 31(15): 5557-5561.

17. Cao H, Chen X, Yang Y, Storm DR (2016) Disruption of type 3 adenylyl cyclase expression in the hypothalamus leads to obesity. Integr Obes Diabetes 2(2): 225-228.