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Journal

Molecular Autism, 12(1)

ISSN

2040-2392

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Publication Date

2021-12-01

DOI

10.1186/s13229-021-00467-1

Peer reviewed

Berg *et al. Molecular Autism* (2021) 12:59
https://doi.org/10.1186/s13229-021-00467-1

Molecular Autism

RESEARCH Open Access

Insulin-like growth factor-2 does not improve behavioral deficits in mouse and rat models of Angelman Syndrome

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Abstract

Background: Angelman Syndrome (AS) is a rare neurodevelopmental disorder for which there is currently no cure or effective therapeutic. Since the genetic cause of AS is known to be dysfunctional expression of the maternal allele of ubiquitin protein ligase E3A (*UBE3A*), several genetic animal models of AS have been developed. Both the *Ube3a* maternal deletion mouse and rat models of AS reliably demonstrate behavioral phenotypes of relevance to AS and therefore offer suitable in vivo systems in which to test potential therapeutics. One promising candidate treatment is insulin-like growth factor-2 (IGF-2), which has recently been shown to ameliorate behavioral deficits in the mouse model of AS and improve cognitive abilities across model systems.

Methods: We used both the *Ube3a* maternal deletion mouse and rat models of AS to evaluate the ability of IGF-2 to improve electrophysiological and behavioral outcomes.

Results: Acute systemic administration of IGF-2 had an effect on electrophysiological activity in the brain and on a metric of motor ability; however the effects were not enduring or extensive. Additional metrics of motor behavior, learning, ambulation, and coordination were unaffected and IGF-2 did not improve social communication, seizure threshold, or cognition.

Limitations: The generalizability of these results to humans is difficult to predict and it remains possible that dosing schemes (i.e., chronic or subchronic dosing), routes, and/or post-treatment intervals other than that used herein may show more efficacy.

Conclusions: Despite a few observed effects of IGF-2, our results taken together indicate that IGF-2 treatment does not profoundly improve behavioral deficits in mouse or rat models of AS. These findings shed cautionary light on the potential utility of acute systemic IGF-2 administration in the treatment of AS.

Keywords: Angelman Syndrome, Ubiquitin, Ube3a, Insulin-like growth factor, IGF, Mouse model, Rat model, EEG, Behavior

Background

Angelman Syndrome (AS) is a rare neurodevelopmental disorder caused by the loss of functional ubiquitin protein ligase E3A [1]. Specifically, AS results from deficient expression of the maternal allele, which leaves the entire brain deficient of UBE3A due to neuron-specific imprinting that silences the paternal allele [2–6]. AS is

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