DOI: 10.1002/alz.062751

DRUG DEVELOPMENT

PODIUM PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

NONHUMAN

BCI-838, an orally active mGluR2/3 antagonist pro-drug, mimics the beneficial effects of physical exercise on neurogenesis, behavior and exercise-related molecular pathways in an Alzheimer's disease mouse model

Mesude Bicak[1] | Georgina E. Perez-Garcia[1,2] | Jacqueline Buros[1,3] | Jean-Vianney Haure-Mirande[1] | Gissel E. Perez[2] | Alena Otero-Pagan[2] | Miguel E. Gama-Sosa[2] | Rita E. DeGasperi[1,2] | Mary Sano[1,2] | Fred H. Gage[4,5] | Carrolee Barlow[4,6] | Joel Dudley[1] | Benjamin S. Glicksberg[1] | Yanzhuang Wang[7] | Benjamin Readhead[8] | Michelle E. Ehrlich[1] | Gregory A. Elder[1,2] | Sam Gandy[1,2]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA

[2]James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA

[3]Generable Inc, New York, NY, USA

[4]BrainCells Inc., La Jolla, CA, USA

[5]Salk Institute for Biological Studies, La Jolla, CA, USA

[6]Escape Bio, South San Fransisco, CA, USA

[7]University of Michigan, Ann Harbor, MI, USA

[8]Arizona State University, Tempe, AZ, USA

Correspondence
Mesude Bicak, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
Email: mesude.bicak@mssm.edu

Abstract

Background: Modulation of physical exercise (PE) represents an intervention that may delay, slow, or prevent mild cognitive impairment (MCI) or dementia due to Alzheimer's disease (AD). One mechanism proposed to underlie beneficial effects of PE involves the apparent stimulation of adult hippocampal neurogenesis (AHNG). BCI-838 is a pro-drug whose metabolite BCI-632 is one of the most active proneurogenic agents known and is an antagonist at group II metabotropic receptors (mGluR2/3). The drug stimulates AHNG while enhancing learning behavior and exerting anxiolytic and antidepressant properties. We previously demonstrated that the administration of BCI-838 to a mouse model of cerebral and cerebrovascular accumulation of oligomeric Ab^{E22Q} (APP^{E693Q} = *"Dutch"*) reduced learning behavior impairment and anxiety, both of which are associated with the phenotype of Thy1.1-*Dutch APP* mice (Kim *et al.*, *Mol Psych* 2014). Herein, we sought to determine whether BCI-838 might substitute for PE, and/or whether treatment with a BCI-838+PE combination might demonstrate synergistic effects in a mouse model of amyloidosis ($APP^{KM670/671NL}$/$PSEN1^{\Delta exon9}$ = *APP/PS1*).

Method: 3-month-old *APP/PS1* mice were treated with either BCI-838, PE (running wheels), or a combination of BCI-838+PE for 1 month. We performed learning behavior tests (novel object recognition and Barnes maze), biochemical, and transcriptomic analyses on the hippocampal dentate gyrus (DG) of *APP/PS1* mice. We performed gene set enrichment analysis, drug repurposing, and chemogenomic enrichment analyses to reveal molecular pathways of interest and investigated compounds with transcriptomically similar profiles as well as drug targets and side effects.

Result: We report that: (i) BCI-838, PE, or BCI-838+PE combination enhanced AHNG, (ii) BCI-838 alone or associated with PE led to improvement in both spatial and recognition learning behaviors, (iii) BCI-838 treatment increased mRNA levels of BDNF, metabotropic glutamate receptors, and PIK3C2A of the PI3K-MTOR pathway, and decreased EIF5A of ketamine-modulating mTOR activity in the hippocampal DG. qPCR results validated the statistical significance of the association between BCI-838 treatment and increased levels of BDNF.

Conclusion: Our study points to BCI-838 as a safe and orally active compound capable of mimicking the beneficial effect of exercise on AHNG, learning behavior, and anxiety in the *APP/PS1* mouse model.