Treatment for Neurodegenerative Diseases such as Alzheimer’s

Using Ryanodine Receptor channel stabilizers to reduce amyloid pathology and normalizing neuronal calcium dyshomeostasis

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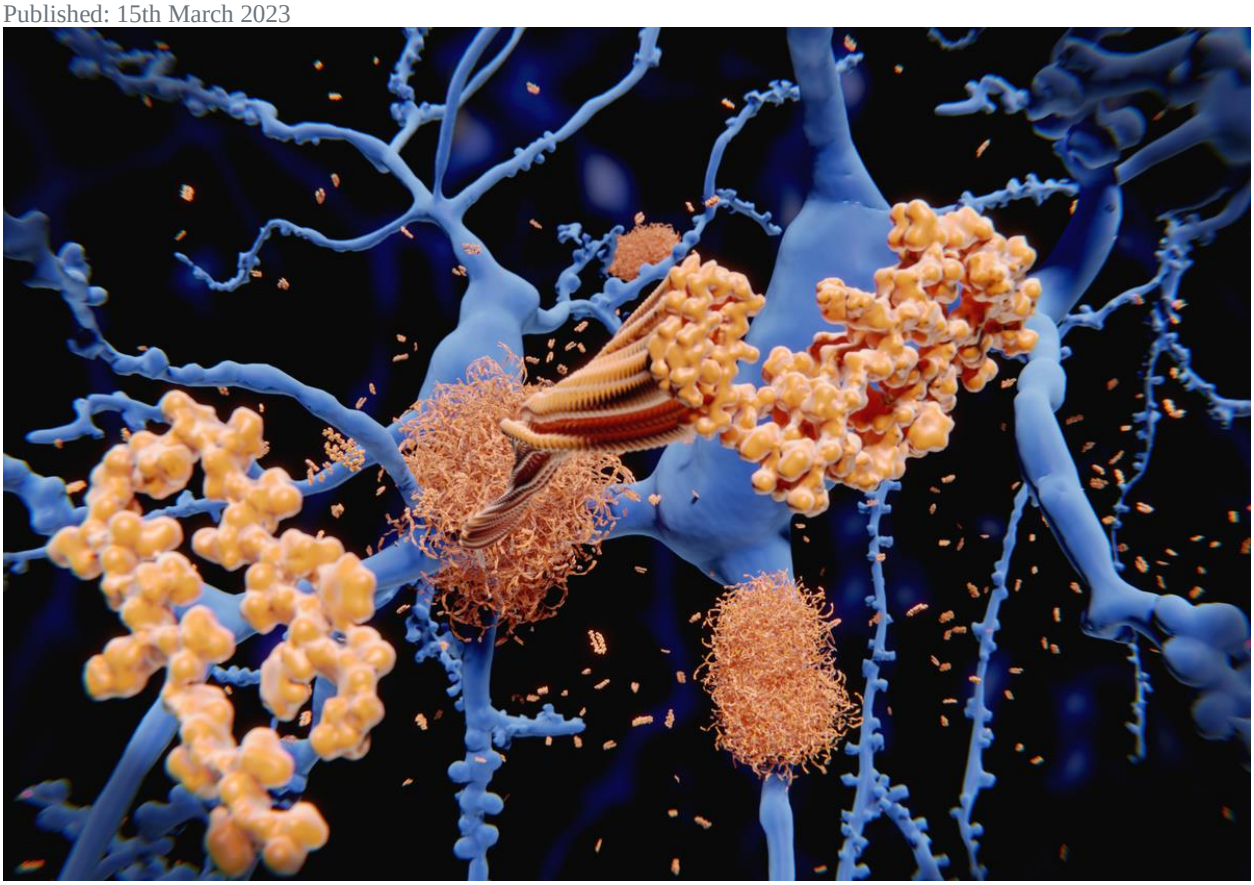

Juan Gärtner, https://stock.adobe.com/uk/images/218190197, stock.adobe.com

Background

Central Nervous System Therapeutics Market was valued at USD 84.24 Billion in 2020 and is projected to reach USD 168.43 Billion by 2028, growing at a CAGR of 9.05% from 2021 to 2028.

Methods and compositions of compounds capable of normalizing neuronal calcium dyshomeostasis for treating neuronal or neurological disorders, including Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, fronto temporal dementia, Pick’s disease, chronic traumatic encephalopathy, traumatic brain injury, stroke, cerebellar ataxia, multiple sclerosis, Down syndrome, and aging-related CNS disorders.

Technology Overview

To date, multiple Phase III clinical trials for the treatment of AD and other neurodegenerative diseases have been unsuccessful, not necessarily because they did not engage their target, but the target may be dissociated from the desired therapeutic outcome, namely retention of cognitive abilities. The majority of the clinical trials for AD therapies have focused on amyloid precursor protein (APP) processing, and while amyloid levels were reduced in many of the clinical trials, there was no positive effect on memory performance.

Ryanodine Receptor-3 Expression and Function in Neurons is well studied. The present disclosure provides compositions and methods comprising novel RyR-targeted small molecule compounds. The disclosure also goes into methods for making these compounds. Treatment with the RyR channel stabilizers disclosed herein normalizes aberrant ER calcium signaling and preserves synaptic functions toward treating neurodegenerative diseases, such as Alzheimer's disease, where RyR channel stabilizers reduce amyloid pathology. Endoplasmic reticulum (ER) calcium signaling is implicated in a myriad of coordinated cellular processes.

The second disclosure focuses on, RyR channel stabilizers reduce amyloid pathology.

The third disclosure also provides synthetic intermediates that are useful in making the compounds. Another aspect of the disclosure provides for pharmaceutical composition comprising a pharmaceutically acceptable carrier, solvent, adjuvant or diluent and one or more compounds. In another aspect, the disclosure provides methods for normalizing neuronal calcium dyshomeostasis in a subject comprising administering to the subject an effective amount of one or more compounds. The disclosure provides methods for treating a neurological or neurodegenerative disorder in a subject comprising administering to the subject an effective amount of one or more compounds. Also, the disclosure provides compositions for treating a neurological or neurodegenerative disorder comprising one or more compounds.

Further Details

- Stutzmann GE, Smith I, Caccamo A, Oddo S, Laferla FM, Parker I. Enhanced ryanodine receptor recruitment contributes to Ca2+ disruptions in young, adult, and aged Alzheimer's disease mice. J Neurosci. 2006 May 10;26(19):5180-9. doi: 10.1523/JNEUROSCI.0739-06.2006. PMID: 16687509; PMCID: PMC6674246.
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- Stutzmann GE. Calcium Dysregulation, IP3 Signaling, and Alzheimer's Disease. The Neuroscientist. 2005;11(2):110-115. doi:10.1177/1073858404270899
- Chakroborty, Shreaya, Goussakov, Ivan, Miller, Megan, Stutzmann, Grace E., Deviant Ryanodine Receptor-Mediated Calcium Release Resets Synaptic Homeostasis in Presymptomatic 3xTg-AD Mice. The Journal of Neuroscience; 2009/07/29; 10.1523/JNEUROSCI.2047-09.2009

Benefits

- Small molecule compound composition and method for synthesis for the treatment of neuronal calcium homeostasis and other neuronal or neurological diseases.
- RyR channel stabilizers reduce amyloid pathology.

Applications

- An alternative approach to treatment of AD and other neurodegenerative diseases is to target aberrant pathogenic calcium signaling cascades. Stabilization of calcium signaling targets a pathogenic mechanism that is tied to many major features and risk factors of Neurodegenerative diseases.
- Compounds and methods for treating neurological diseases by normalizing neuronal calcium dyshomeostasis.

Opportunity

- An exclusive or non-exclusive license
- Research support for additional development

Patents

- US9102645
- US9725429
- US10011578B2

IP Status

- Patented

Seeking

- Licensing

- Development partner