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Abstract

Induction of Seizures from DREADDs in Rodents †

Giovanna F. Oliveira [1], Maria Camila Acero-Castillo [1], Aline Borges [1], Márcia Mortari [2], Patrick A. Forcelli [3,4,5] and Rafael S. Maior [1,2,*]

[1] Laboratory of Neuroscience and Behavior, Department of Physiological Sciences, Institute of Biology, University of Brasília, Brasília 70910-900, Brazil; giovannafernandesdeoliveira@gmail.com (G.F.O.); mcamila-ac@hotmail.com (M.C.A.-C.); eualinecaron@hotmail.com (A.B.)
[2] Laboratory Neuropharma, Department of Physiological Sciences, Institute of Biology, University of Brasília, Brasília 70910-900, Brazil; mmortari@unb.br
[3] Interdisciplinary Program in Neuroscience, Georgetown University, Washington, DC 20057, USA; paf26@georgetown.edu
[4] Department of Pharmacology and Physiology, Georgetown University, Washington, DC 20057, USA
[5] Department of Neuroscience, Georgetown University, Washington, DC 20057, USA
* Correspondence: rsmaior@unb.br
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Introduction: Temporal lobe epilepsy (TLE) is clinically relevant due to its severity and the high percentage of patients resistant to available medications. In the search for more refined and technically and ethically appropriate animal models, the chemogenetic tool called DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) has opened new frontiers in the study of drugs with clinical applications. Therefore, the aim of this study is to develop an animal model of DREADD-induced epilepsy in rodents. Methodology: Phase I: Nine animals, divided into 3 groups (n = 3), were intracerebrally infused with a viral vector for receptor expression in the area tempestas (namely: GiDREADD; rM3D; and hM3D). During testing, the animals received two weekly administrations (1 and 5 mg/kg) of clozapine N-oxide (CNO) for 4 weeks after surgery. Phase II: Eight animals were intracerebrally infused with the viral vector (pAAV-hDix-GiDREADD-dTomato-Fishell-5). In behavioral tests, the animals underwent two tests where the dose of clozapine N-oxide (CNO) was randomized (5 or 10 mg/kg) and one control test. At the end of the experiment, euthanasia and histological analysis were performed. Conclusion: The pAAV-hDix-GiDREADD-dTomato-Fishell-5 vector was able to be bilaterally expressed in the area tempestas, and its activation induced seizures in the experimental subjects, particularly at doses of 5 and 10 mg/kg. The latencies to seizure onset were similar for both CNO doses. To the best of our knowledge based on the available literature, this is the first report of seizure induction via chemogenetics. The project phases were approved by the Animal Use Ethics Committee (CEUA) of the University of Brasília under protocols No. 23106.151489/2022-18 and No. 23106.128947/2023-04.

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