e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2022; 12(4); 67-71

Original Research Article

An Observational Neuropharmacological Analytical Research Study on the Pharmacogenomic Mechanisms of Brain Organoids

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Received: 20-12-2021 / Revised: 28-01-2022 / Accepted: 22-02-2022
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Conflict of interest: Nil

Abstract

Introduction: Brain organoids recapitulate *in vitro* the specific stages of *in vivo* human brain development, thus offering an innovative tool by which to model human neurodevelopmental disease. Brain organoids can model congenital structural deficits or be subjected to environmental insult.

Objectives: The objective of this study was an observational analytical molecular neuropharmacological research study on the pharmacogenomic mechanisms of brain organoids.

Methods: In this study, at first, the records were identified, through database searching. The additional records were identified through other sources, which included the screened records, after the irrelevant studies were removed. From these screened records, few records were excluded, as per the exclusion criteria. Then, the full text articles were assessed for eligibility, from which few full text articles were excluded, according to the exclusion criteria, with adequate reasons. Then, rest of the studies were included, according to the inclusion criteria for the neuropharmacological analytical research study on the pharmacogenomic mechanisms of brain organoids. An observational analytical molecular neuropharmacological research study was also conducted.

Results: This descriptive observational analytical research study described the molecular neuropharmacological and pharmacogenomic mechanisms of brain organoids, which elaborated this molecular pharmacological research analysis.

Conclusions: To conclude, this observational clinical research provided a descriptive analysis on the pharmacogenomic mechanisms of brain organoids.

Keywords: Brain Organoids, Pharmacogenomics, Pharmacology, Neuropharmacology, Analytical Clinical Research.

Introduction

Organoids are three-dimensional cell structures, grown *in vitro* from the stem cells, mainly isolated from the biopsies or from the pluripotent stem cells, that are extensively similar to the endogenous organs, in both their structural development and functional performance. The organoids are formed of cells which differentiate, undergo spatially

restricted lineage commitment, and acquire the specific tissue patterning to develop into several endoderm, mesoderm, and ectoderm-derived tissues. These organoids mostly tend to resemble the *in vivo* original organs, with the preservation of their genetic, phenotypic and behavioural traits. These are not only complex structures, but also possess unique capabilities of modeling human organ development and disease, showing wide similarities with the human organ system.

Brain organoids recapitulate *in vitro* the specific stages of *in vivo* human brain development, thus offering an innovative tool by which to model human neurodevelopmental disease. Brain organoids can model congenital structural deficits or be subjected to environmental insult[1-7].

This neuropharmacological clinical research was conducted for exploring the pharmacogenomic mechanisms of brain organoids, with thorough explanations and analysis of the medical study literature and evidences compiled from the different studies conducted, thus illuminating on the pharmacomolecular mechanisms of brain organoids.

Objective:

The objective of this study was a neuropharmacological analytical research on the pharmacogenomic mechanisms of brain organoids.

Materials and Methods:

Ethical principles

The study was conducted in accordance with the ethical principles of Declaration of Helsinki and Good Clinical Practices, contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6 and ICH-E17), and in compliance with the global regulatory requirements, as well as the regulatory frameworks and general guidelines required for organoids and their clinical applications, for example, drug testing using organoids in Europe, include "Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches" by the European Medicines Agency, the regulatory requirements for cell and gene-based therapies, and good manufacturing practices (GMP) of a pharmaceutical drug, for the clinical use of organoids.

Study Type

This study was a multi-variate, observational, descriptive, analytical, qualitative molecular neuropharmacological research study on the pharmacogenomic mechanisms of brain organoids.

Study Materials

The study materials consisted of pharmacological clinical research database of global heterogenous research analyses and similar study literature on the pharmacogenomic mechanisms of brain organoids.

Study Period

The study period for this research project and the compilation of the study literature was 1 year, from March, 2021 to March, 2022.

Place of Study

This research study and the compilation of the study literature was conducted in the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacoepidemiology, Pharmacovigilance, Pharmacogenomics, Evidence-Based Medicine, Clinical Pathology, Molecular Diagnostics, Clinical Medicine, Regenerative Medicine, Organ Transplantation and Clinical Research, at Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Rama Medical College Hospital and Research Centre, Rama University, Mamata Medical College and Hospitals, Fortis Hospitals,

Global Institute Of Stem Cell Therapy and Research (GIOSTAR), Institute of Regenerative Medicine (IRM), Institutes, Hospitals and Laboratories, All India Institute of Medical Sciences, Rama Medical College Hospital and Research Centre, and Rama University.

Study Procedure

In this study, at first, the records were identified, through database searching. The additional records were identified through other sources, which included the screened records, after the irrelevant studies were removed. From these screened records, few records were excluded, as per the exclusion criteria. Then, the full text articles were assessed for eligibility, from which few full text articles were excluded, according to the exclusion criteria, with adequate reasons. Then, rest of the studies were included, according to the inclusion criteria for the neuropharmacological analytical research study on the pharmacogenomic mechanisms of brain organoids. An observational analytical molecular neuropharmacological research study was also conducted.

Results:

From the compilation of pharmacotherapeutic databases and evidences and the observational analytical molecular neuropharmacological research study, the pharmacogenomic mechanisms of brain organoids was described, in complete details, to elaborate on the qualitative details of the conducted neuropharmacological clinical research.

Discussion:

From the compilation of the pharmacotherapeutic databases and evidences and the observational analytical molecular neuropharmacological research study, the following details were described.

Genetic engineering and multi-organoid fusion enable the assessment of a broader array of disease mechanisms, such as abnormal interregional development. Various methods can be used to evaluate the developmental changes that underlie the disparate phenotypes observed between normal and diseased organoids. Perhaps the greatest application of brain organoid technology thus far, in vitro modeling of neurodevelopmental disease enables observation of disease progression throughout neurodevelopment and—in conjunction with novel genetic techniques—the opportunity to interrogate underlying pathological mechanisms with previously precluded precision. The versatility of brain organoids permits modeling diseases of either intrinsic (i.e., genetic) or extrinsic (i.e., environmentally mediated) etiology. However, despite recent characterization of functional network development, developmental disorders in which gross structural abnormalities predominate remain the more accessible for in vitro modeling. Autosomal recessive primary microcephaly (MCPH) has been modeled with organoids generated from patient-derived iPSCs carrying mutations in either ASPM, the gene that codes for a protein involved with mitotic spindle function and that accounts for a plurality of MCPH cases, or CDK5RAP2, a gene whose product localizes to the mitotic spindle pole during neurogenesis. Those iPSCs in which ASPM expression was downregulated, predicted to impede neural progenitor proliferation, yielded hypoplastic organoids with fewer proliferative cells, decreased neocortex-like morphology, and diminished neuroepithelial structural integrity. Functional analysis revealed calcium activity in fewer cells than the controls—implicating neuronal maturation impediment—and decreased synchrony. CDK5RAP2-mutant organoids likewise portrayed hypoplasticity with sparse progenitor and neuroepithelial regions. Coincident findings of premature neural differentiation and increased neuron quantity were supported by observation of increased neuronal differentiation upon CDK5RAP2 RNAi-knockdown. Successful phenotypic

rescue upon electroporated expression of CDK5RAP2 protein confirmed viable in vitro recapitulation of MCPH.

In several studies, the demonstration of various types of transient and stable approaches for genetic modifications in the brain organoids, have been visualised. The techniques, as per the stage of development for multi-dimensional applications, include Cas9 nickase KO, Cas9 oligonucleotide knock-in, TALEN inducible gene knock-in, PiggyBac fluorescence and lentivirus fluorescence approaches, at single cell stage, all of which were stable; Sleeping Beauty nucleofection and CRISPR/Cas9 KO nucleofection approaches, at embryoid bodies stage, all of which were stable; adeno-associated virus fluorescence, plasmid gene rescue, plasmid fluorescence, shRNA approaches, at organoids stage, all of which were transient; and lentivirus fluorescence, viral stamping, Cas9 oncogene knock-in and suppressor KO and Sleeping Beauty GFP approaches, at organoids stage, all of which were stable, manifested various degrees of mosaicism and spatial distribution of genetically modified cells, following the above-mentioned types of transfection and genetic modification approaches.

The ultimate application of organoid technology is to use them for organ regeneration and replacement therapies, reducing whole organ transplant requirements and improving the life quality of patients. Organoids should highly impact regenerative treatments of organs that remain technically non-transplantable, such as the brain. The recent development of edited pluripotent stem cells with targeted disruption of HLA genes by CRISPR/Cas9 technology should also facilitate the generation of immune-compatible healthy organoids for widespread therapeutic purposes[1-7].

This neuropharmacological analytical clinical research study provided the analytical elaborations on the unique complexities of the pharmacogenomic mechanisms of the brain organoids.

Conclusion:

To conclude, this study analytically describes the pharmacogenomic mechanisms of brain organoids, which comprehensively clarified and elaborated the various functional neuropharmacological perspectives.

Acknowledgements:

My gratitude to the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacoepidemiology, Pharmacovigilance, Pharmacogenomics, Evidence-Based Medicine, Clinical Pathology, Molecular Diagnostics, Clinical Medicine, Regenerative Medicine, Organ Transplantation and Clinical Research, at Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Rama Medical College Hospital and Research Centre, Rama University, Mamata Medical College and Hospitals, Fortis Hospitals, and Global Institute Of Stem Cell Therapy and Research (GIOSTAR), Institute of Regenerative Medicine (IRM), Institutes, Hospitals and Laboratories, All India Institute of Medical Sciences, Rama Medical College Hospital and Research Centre, Rama University, and, the global electronic medical literature databases, for the successful completion of this clinical research project.

Funding Sources: No funding sources for this research project.

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