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Description of the funded research project

1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and Procure High-Value Research Equipment

Title of the research project: GPER1 neuroestrogen membrane receptor: a novel, rapid-acting, promising target for psychopharmacology

Principal Investigator: Christina Dalla, Associate Professor of Pharmacology, Medical School of Athens, NKUA

Reader-friendly title: Investigating a novel, rapid-acting, promising target for gender-oriented psychopharmacology

Scientific Area: Life Sciences, Medical and Health Sciences

Host Institution: National and Kapodistrian University of Athens (NKUA), Medical School, Department of Pharmacology, Neuropsychopharmacology Research Group

Collaborating Institution(s): ICVS Institute at the Medical School of University of Minho in Portugal

Project webpage: http://psychopharmacology.med.uoa.gr/

Budget: € 180000

Duration: 36 months

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Research Project Synopsis

Affective disorders pose a major burden in modern western societies and women are twice as vulnerable as men. Currently available pharmacotherapies focus on enhancing the monoaminergic neurotransmission, but recovery requires several weeks. Recent findings link rapid neuroestrogen signaling with depression/anxiety and the newly-identified G protein-coupled estrogen receptor 1 (GPER1). Furthermore, it seems that the unique rapid antidepressant mechanism of action of the glutamatergic agent, ketamine, shares striking similarities with the neuroestrogen-mediated GPER1 rapid signaling. In this proposal, we aim to understand the role of GPER1, which could reveal novel therapeutic pathways for the faster and better treatment of mood disorders in men and women. Secondly, we aim to investigate whether GPER1 activation mimics the rapid effects of ketamine. To accomplish these objectives a series of experiments on male and female rats are proposed for a period of 36 months. First, we will investigate whether the GPER1 over/under-expression, with genetic manipulations, exerts antidepressant/anxiolytic effects. Secondly, we will compare the behavioral and neurobiological effects of GPER1 over/under-expression with the rapid effects of GPER1 agonists/antagonists injected locally in the hippocampus. Subsequently, we will identify the molecular pathways involved in rapid GPER1 activation in the circuit hippocampus-prefrontal cortex. Moreover, we will determine whether GPER1 antagonism inhibits the rapid effects of ketamine and the well-known antidepressant/anxiolytic effects of sertraline. Lastly, we will investigate whether GPER1 chronic activation induces a sustained antidepressant effect or augments the action of sertraline, using the chronic mild stress model of depression. Our proposed studies, building on our previous observations on sex differences in models of depression, will contribute to the elucidation of the underlying mechanisms of neuroestrogens. Moreover, they may lead to the identification of a novel target, whose pharmacological agonism could lift depression within hours, thus, dramatically improving the quality of life for millions of patients worldwide.

Project originality

Mood disorders and anxiety pose a significant burden in western societies and especially in women who suffer more often than men. In addition, women experience gender-dependent disorders such as postpartum depression and premenstrual syndrome. Pharmacotherapy for depression and anxiety is based on drugs that alter monoaminergic neurotransmission, but require several weeks of treatment to work, and are not effective in 35% of patients. While a systematic effort is being made to discover new antidepressants, research to date has failed, mainly due to the unknown exact etiology of these disorders. Given the greater impact of mood disorders and stress on women, the role of estrogen in the symptomatology, pathology, and treatment of disorders has been extensively studied. In particular, their administration during the perimenopausal period improves the depressive symptoms while in the menopause there is a reduced response to antidepressants. However, estrogen administration has been shown to be particularly complex, with both positive and negative effects and ultimately without clinical utility. This research project proposes for the first time the complete investigation of a G-protein-conjugated estrogen receptor (GPER1). According to recent research, the direct effects of neuroestrogens on the brain are now thought to be through the aforementioned receptor. This receptor appears to be essential for the "micro-regulation" of neural circuits involved in depression and stress. Therefore, the primary purpose of the present study is to develop knowledge about GPER1 as a new therapeutic target for faster treatment of mood disorders in male and female patients. A secondary purpose is to understand the common mechanisms of action of GPER1 and glutamate drugs (e.g. ketamine) under study for rapid antidepressant action, and to investigate the potential for potentiation of GPER1 in the widely used serotonergic drugs.

Expected results & Research Project Impact

This project takes a measured risk to focus on a novel candidate target aiming to alleviate depression within hours, thus, dramatically improving the quality of life for millions of patients. Neuroestrogens are also involved in several other debilitating disorders that present sex differences (e.g. autism, Alzheimer's, Schizophrenia, and Parkinson's diseases) or are specific to women. This project will elucidate neurosteroid mechanisms that may enhance our understanding and potential treatment of these diseases, as well. Moreover, the National Institute of Health has issued guidelines for the use of female animals in preclinical research and the scientific community aims towards sex-specific psychopharmacology. Our group has repeatedly shown the presence of sex differences in animal models of depression and anxiety. This project will identify sex differences that could both promote our basic knowledge about affective disorders and/or influence treatment response. The potential social impact is of paramount importance as affective disorders burden millions of Europeans and are associated with immense financial and social costs. Especially for women, the burden caused by depression in 2010 was more than any other neurological or psychiatric disorder. Our study will be relevant to both men and women suffering from depression that costs more than 200 disability adjusted life years per 10.000 persons in the European economy. Worldwide, more than 300 million people live with depression, a staggering increase of over 18% between 2005 and 2015. Moreover, workplace costs associated with depression-related disability and suicidal behavior further add to the global burden of the disease. A further benefit of this study is that the generation of high-quality preclinical research with translational potential will also benefit the national and international pharmaceutical industry.

The importance of this funding

Funding studies in the field of Neuropsychopharmacology can help us understand, fight and overcome diseases, strengthen the economy and, most importantly, improve the world for all. A variety of neurological and neuropsychiatric diseases are major challenges that humans and society as a whole face, and require time, dedication, vision, along with advanced technologies, collaborations, and the ability to communicate with colleagues to find new therapies. All of the above require financial support through funding opportunities to ensure high quality research. It is important to emphasize that adequate funding opportunities can improve research quality and reduce failures and related future financial costs. They also contribute to the education of students and the prosperity of the Greek University. Besides, Associate Professor Christina Dalla actively contributes to the preclinical data network of the European College of Neuropsychopharmacology, which aims to improve the quality of preclinical research.

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