BIOMEDICAL & VETERINARY SCIENCES

GRADUATE PROGRAM

ANNOUNCES

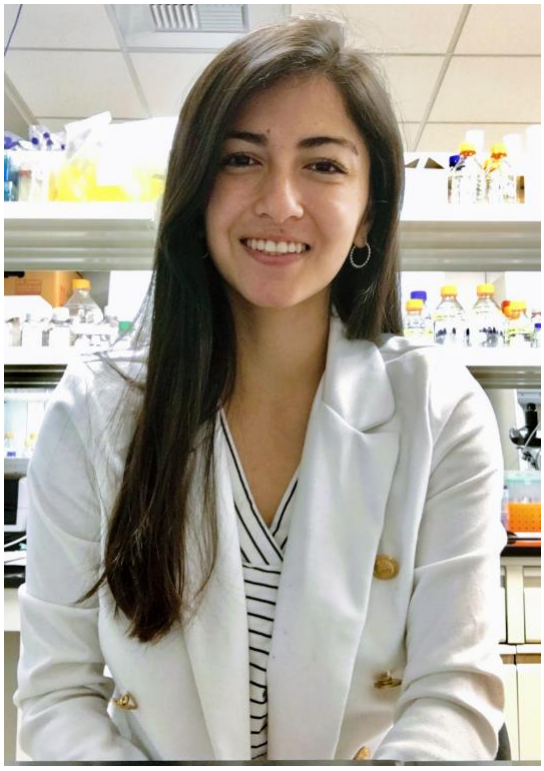
The Master of Science Seminar and Examination of

Lina Cortes Kwapisz

“Pharmacology of a novel biased allosteric modulator for NMDA receptors”

Wednesday, April 28th, 2021
1:00 PM
Zoom link: https://virginiatech.zoom.us/j/81166422935

Bio



I was born in the countryside of Colombia and from a young age I developed a passion for animals. With my father's support, I completed my bachelors in veterinary medicine in La Salle University. Once I graduated I had several jobs that included workingas an equine intern doctor and veterinary radiology director of operations. Seeking new cultural experiences and learning opportunities, my twin sister, Camila, and I came to the U.S. and met the loves of our lives, getting married just one week apart from each other.

My desire to expand my research knowledge motivated me to applied for the BMVS master's program at Tech. Completing a masters degree has been a huge learning experience and I'm beyond grateful to everyone that have helped me along the way. In the future, I plan to do an internship at the EMC and plan on continuing onward to complete my residency. My goal is to become an equine surgeon and go back to my home country to help others achieve their academic goals. I'm thankful for where I am currently, and I'm excited for what comes next.

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Lay Language Abstract

NMDA glutamate receptor is a ligand-gated ion channel that mediates a major component of excitatory neurotransmission in the central nervous system (CNS). NMDA receptors are activated by simultaneous binding of two different agonists, Glutamate and glycine/ D-serine1. With aging, glutamate concentration gets altered, giving rise to glutamate toxicity that contributes to age-related pathologies like Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and dementia. Some treatments for these conditions include NMDA Receptor blockers like memantine. However, when completely blocking the receptors, there is a restriction of the receptor's normal physiological function59. A different approach to regulate NMDAR receptors is thorough allosteric modulators that could allow cell type or circuit-specific modulation due to widely distributed GluN2 expression without global NMDAR overactivation.

In this study, we hypothesized that the compound CNS4 selectively modulates NMDA diheteromeric receptors (GluN2A, GluN2B, GLuN2C, and GluN2C) based on three different glutamate concentrations. Electrophysiological recordings carried out on recombinanat NMDA receptors expressed in xenopus oocytes revealed that 30μM and 100μM of CNS4 potentiated the GluN2C and GluN2D subunits with 0.3μM Glu/100μM Gly. However, when using 300μM Glu/100μM Gly, CNS4 inhibited the relative response in the GluN2D subunit and no effect on the remaining subunits. CNS4 does not replace either glutamate or glycine and needs both to significantly increase or decrease NMDAR relative response. In order to understand the I-V curve of CNS4, another set of electrophysiological recordings was made. Presence of 100μM CNS4 increased the ions inward current through the channel pore with more positive membrane potential values in the GluN2C and GluN2D subunits, the GLuN2C subunit was the only with change in reversal potential of permeant ions. Compounds that are voltage independent are preferred since can act equally at all physiological membrane potentials. CNS4 had no voltage dependent effect with any glutamate concentration.

Finally, to understand the effect of CNS4 in neuronal viability, we have performed excitotoxicity assay using rat brain cortical and striatal neurons. Primary rat brain neuronal culture was made in two brain regions, cortex and striatum. Increasing doses of NMDA with constant 100μM CNS4 increased cellular Ca2+ influx in a dose-dependent manner. Particularly, 100μM CNS4 with 300μM NMDA exhibited a significant increase in Ca2+ influx in both cortex and striatum regions

compared to NMDA alone treatment. However, when used alone, 100µM CNS4 did not have an effect on the amount of Ca2+ influx. Correspondingly, the increase in Ca2+ was nontoxic for neurons since the metabolic activity of primary neurons was not altered in the presence of 100 µMCNS4.

Publications

Martinez, C., Cortes, L. Cepeda, L. Munoz, L, Soler, D. (2014) Preliminary study of Puma concolor behavior, as a welfare indicator in two Cundinamarca Zoos in Colombia. Journal: Notes from an Internal Medicine Conference on Exotic and Non-Conventional Wildlife Studies, 10 (1), 11-24

Presentations

Kwapisz L, Mehrkens B and Costa B (2021) Pharmacology of a novel biased allosteric modulator for NMDA receptors. 31st Annual BMVS Graduate Research Symposium. Virginia Tech, Blacksburg, VA.

Vacca B, Johnston T, Kwapisz L, Bledsoe D, Wagner A, Costa B. (2019) A Biased Allosteric Modulator Separates Triheteromeric (GluN1/2A/2B) from Diheteromeric (GluN1/2A) NMDA Receptor. 7th Annual Drug Discovery Da. Virginia Tech, Blacksburg, VA.

Vacca B, Johnston T, Kwapisz L, Bledsoe D, Wagner A, Costa B. (2019) A Biased Allosteric Modulator Separates Triheteromeric (GluN1/2A/2B) from Diheteromeric (GluN1/2A) NMDA Receptor. 30th Annual BMVS Graduate Research Symposium. Virginia Tech, Blacksburg, VA.

Examination Graduate Committee

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