# Modulation of Synaptic AMPA Receptors by Polysialic acid: Potential Future Therapeutics for Neurodegenerative Disorders

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As the legal use of recreational marijuana changes, women have increasingly begun to use marijuana to reduce morning sickness while pregnant. The long-term effects that this prenatal exposure has on the fetus are unknown. The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) subtype of glutamate receptors mediates fast excitatory neurotransmission in the mammalian central nervous system and is implicated in memory impairment associated with several neurodegenerative disorders. Hence it is highly possible that this is one of the subtypes being affected due to prenatal exposure, causing slower reflexes and impaired memory. Carefully controlled modulation of AMPA receptors is critical for normal synaptic transmission. Several endogenous molecules play a vital role in regulating the functional properties of AMPA receptors. Polysialic acid (PSA), a highly negatively charged carbohydrate, covalently attached to the neural cell adhesion molecule (NCAM), is extensively expressed in hippocampal synapses and alters the single-channel properties of AMPA receptors. However, the effects of PSA on native synaptic AMPA receptors have never been investigated. This study utilized biochemical isolation and functional reconstitution of synaptosomal AMPA receptors in lipid bilayers to elucidate the effects of PSA on synaptic AMPA receptors. PSA, in a concentration-dependent manner, increases the single-channel open probability and mean open time, and decreases the mean closed time (Figure 1).

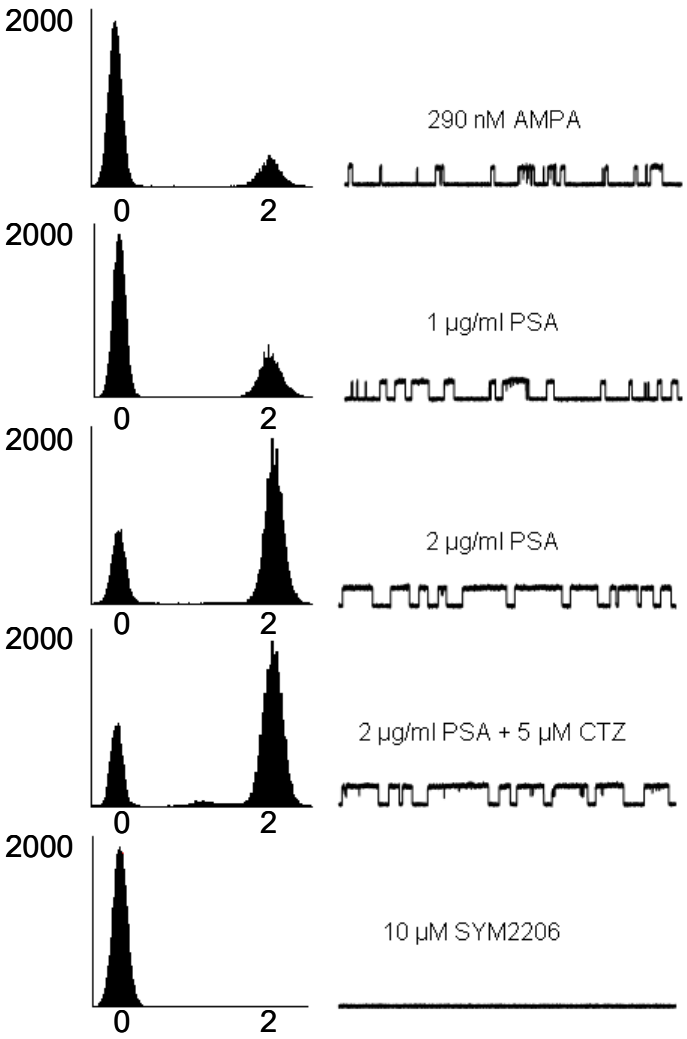


**Figure 1: Modulation of Synaptosomal AMPA Receptors by PSA.** *Channel openings are indicated by upward transitions of the current. (A-E) represent average amplitude histograms (left) and the respective average trace (right) recorded in the presence of 290 nM AMPA (A), addition of 1 µg/ml PSA (B), 2 µg/ml PSA (C), and 2 µg/ml PSA + 5 µM CTZ (D). In (E) activity was blocked with the specific AMPA*

*receptor antagonist, SYM2206 (10 μM). All recordings were done at +75 mV. The amplitude histograms show bimodal distributions with peaks corresponding to the stationary current levels (i.e. open and close states). The maximum unitary current was 2.1 pA. The channel conductance was 28 pS.*

The results indicate that PSA potently modulates synaptic AMPA receptors. Modulation of AMPA receptors is a possible strategy to ameliorate memory deficits in neurodegenerative conditions. Therefore, molecules derived from PSA could be a potential therapeutic option to treat memory loss in neurodegenerative diseases.

Understanding the effects of prenatal exposure to marijuana (THC) on AMPA receptors is necessary before exploring the idea that PSA could be potentially therapeutic. Literature suggests that rodents exposed to THC have impaired memory. Since AMPA receptors are implicated in memory formation and storage, their role in prenatal THC exposure mediated memory impairment needs to be thoroughly investigated. The role of PSA with regards to its interaction with AMPA receptors can then be therapeutically exploited to rescue such memory deficits.

## Statement of Research Advisors

Ms. Lucy Seay contributed to experimentation related to the work originally found and conceptualized by Dr. Sims. Lucy took great endeavor in understanding the complex experiments and concepts.
*- Drs. Subhrajit Bhattacharya and Vishnu Suppiramaniam, College of Pharmacy, Auburn University*

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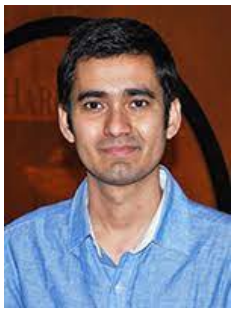
## Authors Biography

Lucy Seay is a sophomore-year student pursuing a B.S. degree in Computer Science from the college of engineering at Auburn University. Following her undergraduate graduation, she hopes to attend medical school and practice as a pediatric surgeon.

Dr. Catrina Robinson is the associate professor of neurology at the Medical University of South Carolina. Dr. Robinson is focused on understanding the impact of metabolic disorders on both normal and pathological brain aging.



Dr. Subhrajit Bhattacharya is an assistant research professor at Auburn University's Harrison School of Pharmacy in the department of drug discovery and development. Dr. Bhattacharya's lab investigates neuronal circuits and synapses with a primary focus on the effects of epilepsy, stroke, prenatal use of substances of abuse, AD, and neurodegeneration.

Dr. Vishnu Suppiramanian is the director of research development and support, co-director of the center for neuroscience initiative, Gilliland endowed professor at Auburn's Harrison School of Pharmacy in the Department of Drug Discovery and Development. Dr. Suppiramaniam is responsible for leading the school's research program, infrastructure, and graduate student training programs.