NMDA Receptor Inhibition Prevents Intracellular Sodium Elevations Induced by the Sodium Ionophore Monensin in Human Olfactory Neuroepithelial Precursors Derived from Bipolar Patients

Rif S. El-Mallakh, MD,1 Yonglin Gao, MD,1 Aaron Mack, MD,1 Nick Delamere, PhD,2
1Department of Psychiatry, University of Louisville School of Medicine, Louisville, Kentucky
2Head, Department of Physiology, University of Arizona, Tucson, Arizona

INTRODUCTION

▪ The lifetime prevalence of comorbid alcohol use disorder in patients with bipolar illness exceeds 60%
▪ We have previously reported that ionic disturbances caused by glutamate in neuronal cells derived from subjects with bipolar disorder are corrected by lithium or ethanol (EtOH), but only in cells from bipolar individuals and not in cells from non-bipolar controls
▪ We examined NMDA receptor function in these cells in response to a non-glutamate ionic stress.

RESULTS

▪ Monensin alone significantly increased [Na]i in ONPs from bipolar individuals (5.08 ± 0.71 vs baseline 3.13 ± 0.93, P =0.03) and AP5 had no effect (2.0 ± 1.2 vs baseline 3.13 ± 0.93, P =0.27).
▪ The combination of AP5 and monensin resulted in normalization of [Na]i (3.25 ± 1.28 vs baseline 3.13 ± 0.93, P =0.89).
▪ This effect was not observed in cells from non-bipolar individuals (monensin alone, 1.72 ± 1.10 vs baseline 2.42 ± 1.80, P =0.25; AP5 alone 2.10 ± 1.10 , AP5 combined with monensin, 1.53 ± 0.98 vs baseline 2.42 ± 1.80, P =0.31).

METHODS

▪ Olfactory neuroepithelial precursors (ONPs) were obtained by biopsy from type I bipolar patients and non-bipolar controls matched for age, gender, and passage number (n=3 and n=6, respectively).
▪ ONPs were cultured in MEM, gentamycin 0.1mg/mL and FBS 10%, in 5% CO2. ONPs in culture produce neurons, glia, and undifferentiated neural precursor cells. ONPs were treated with, 1 µM monensin (sodium ionophore) for 6 hours, 0.1mM AP5 (NMDA glutamate binding site receptor antagonist) for 6 hours, Or pretreated AP5 30 minutes followed by monensin for 6 hours.
▪ Intracellular sodium ([Na]i) was measured with flame spectroscopy and expressed as concentration per protein as measured by Lowery.

DISCUSSION & CONCLUSION

▪ ONPs derived from bipolar individuals are more susceptible to [Na]i elevations induced by monensin compared to controls
▪ Blockade of NMDA glutamate binding site with AP5 prevents elevations of [Na]i and normalizes response to sodium ionophore monensin
▪ NMDA receptor appears necessary for bipolar-specific sodium ion dysregulation