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Ethanol normalizes glutamate-induced elevation of intracellular sodium in olfactory neuroepithelial progenitors from subjects with bipolar illness but not nonbipolar controls: Biologic evidence for the self-medication hypothesis

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Keywords

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1 | INTRODUCTION

Alcohol use disorders are quite common in bipolar patients with a prevalence of comorbidity that exceeds all other primary psychiatric diagnoses other than other substance use disorders¹; over 60% of people with bipolar disorder type I (BD I) have comorbid alcohol dependence at some point in their lives.¹ This intimate relationship has served as the basis of the proposed idea of “self-medication.”² However, biological confirmation of “self-medication,” specifically, the correction of an abnormal biologic marker with alcohol, has never been demonstrated.

Recently, we have succeeded in utilizing olfactory neuroepithelium biopsy to produce permanent cell lines of olfactory neuroepithelial progenitors (ONPs) from patients with BD and matched nonbipolar controls.³ These cells possess the genetic heritage of BD I and can be used for investigation of differential biological responses to ethanol.

Ionic regulatory abnormalities have repeatedly been documented in patients with BD I.⁴ Most notably, intracellular sodium and calcium are elevated during both mania and depression, this distribution of cations alters transmembrane potential of lymphocytes—a phenomenon which may be a useful diagnostic marker (reviewed in references 4). Both pharmacologic and genetic animal models which inhibit the sodium pump to elevate intracellular sodium and calcium concentrations create mania-like behaviors (reviewed in 4).

Similarly, altered-glutamate metabolism is a consistent finding in BD (reviewed in 4). Importantly, brain glutamate and glutamine are elevated in most brain areas in patients with bipolar illness during mania, depression, and euthymia. By extension, treating ONP cells with glutamate to increase both intracellular sodium and calcium may be a cellular model of bipolar illness, mania, and/or bipolar depression.

2 | RESULTS

MSG alone at 0.1 M, and ethanol alone at 0.05 M for 6 hours were associated with a significant increase $[Na]_{in}$ in both patients and controls (both $P < 0.05$) (Figure 1). MSG 0.1 M for 0.5 h followed by ethanol 0.05 M (and continued MSG exposure) for 6 h, or MSG 0.1 M for 0.5 h followed by lithium 1 mM (and continued MSG exposure) for 6 h, both normalized the elevation of $[Na]_{in}$, but only in ONPs from BD I subjects and not in non-BD-derived ONPs (Figure 1).

3 | DISCUSSION

The current data appear to provide the first biological biologic evidence by which ethanol may indeed result in “self-medication” in BD I. We utilized neuronal progenitor cells that spontaneously differentiate into neurons and glia, that have the genetic heritage of BD.³ We further modeled illness in this disorder by adding glutamate and increasing $[Na]_{in}$ and calcium as occurs in ill bipolar patients.^{3,4} In this cellula model lithium and ethanol both normalize $[Na]_{in}$ similarly in cells obtained from subjects with bipolar illness (Figure 1).

It is important to note that when ONPs derived from subjects with BD I were exposed to ethanol alone, $[Na]_{in}$ increased to the same degree as exposure to glutamate alone, and in a way similar to ONPs from nonbipolar controls (Figure 1). These results suggest that while ethanol may ameliorate the effects of excessive glutamate, it has the opposite effect when glutamate is not present. Translating these findings are to the clinical situation tentatively suggests that ethanol use may be associated with amelioration of symptoms if a patient with bipolar illness is actively ill, but its use would be expected to worsen clinical presentation if consumed by euthymic bipolar subjects. It is clearly a big jump from cells in culture being treated with glutamate, ethanol, and lithium, to humans with mania drinking ethanol. However, the data clearly demonstrate that cells obtained from bipolar individuals and nonbipolar controls respond very differently to ethanol when co-treated with glutamate, and that the effect of ethanol is very similar to the effects of lithium (Figure 1).

Both bipolar depression and bipolar mania are associated with elevated $[Na]_{in}$ compared to euthymia,⁴ and elevations of glutamate in multiple brain regions have been repeatedly demonstrated in BD I. The current study attempted to model this by treating the neural ONP cells with glutamate. This type of in vitro modeling resembles the creation of behavioral animal or physiologic models of mania or cycling,⁴ and is similar to other attempts to understand the pathophysiology of bipolar illness at the cellular level.⁵ Such studies ultimately help shed light on the physiology of the disorder.

Conclusions are further limited by the small sample size. However, the labor-intensive nature of working with ONP cells, or the related induced pluripotent stem cells, is recognized with some acceptance of small sample sizes.⁵

The role of alcohol use to relieve affective symptoms in patients with BD, as self-medication, is controversial. Patients generally report that they consume substances for the same reasons as nonbipolar subjects.³ On the other hand, motivation for ethanol consumption is different during different mood states.³ Clinical outcomes (worsening of the course of the illness), and self-report do not always support self-medication hypothesis. However, the current data appear to provide a neurobiological mechanism by which ethanol may indeed result in “self-medication” in BD I.

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Cases

Three ONP cell lines from BD I subjects (a 23-year-old male; a 53-year-old male; and a 43-year-old female), and six from gender- and age-matched nonbipolar subjects (a 21-year-old male; a 47-year-old male; and a 40-year-old female a 21-year-old male; a 45-year-old male; and a 40-year-old female) were used in this study. Only one patient (the 47-year-old male) had a history of alcohol use disorder. Monosodium glutamate (MSG) was used at 0.1 M in order to model the elevation of intracellular sodium concentration ($[Na^+]_{in}$) seen in bipolar patients, which is generally two to three times baseline.^{3,4} Ethanol was examined at the clinically relevant concentration of 0.05 M (equivalent to 0.292 mg/dL, and below the LD₅₀ of 0.5 mg/dL). Lithium was utilized at therapeutic levels of 1 mM. All treatments were carried on for 6 h because this duration is associated with the stability of changes (data not shown). $[Na]_{in}$ was measured with flame spectroscopy per cellular protein concentration measured by Lowry methodology. Data are expressed as fold change from baseline and analyzed with paired and unpaired 2-tailed *t* tests.

Key message

In this study of olfactory neuroepithelial progenitor cells from patients with and without bipolar I illness we demonstrate the first biologic evidence that ethanol normalizes neuronal abnormalities induced by excitotoxicity in a manner similar to lithium only in cells from patients with bipolar illness.

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FIGURE 1.

Treatment with either 0.1 M monosodium glutamate (MSG) or 0.05 M EtOH alone for 6 h increased $[Na]_{in}$ to a similar degree in both bipolar disorder type I (BP) ($2.3 \pm SD 0.62$ and 2.1 ± 0.18 fold vs. baseline, respectively) and non-BP subjects (2.19 ± 1.4 and 2.97 ± 2.2 fold vs. baseline, respectively). Treatment with 1 mM Li alone for 6 h did not change $[Na]_{in}$ compare to baseline. Treatment with MSG followed by Li normalized $[Na]_{in}$ in BP only (0.65 ± 0.07 fold vs. baseline) but not non-BP cells (2.42 ± 1.1 fold vs. baseline; $P = 0.03$). Treatment with MSG followed by EtOH also normalized $[Na]_{in}$ in BP (0.7 ± 0.28) but not non-BP cells (1.7 ± 0.76 fold vs. baseline, $P = 0.02$ * < 0.05)