



# Sodium Butyrate Protects Against Ethanol-Induced Toxicity in SH-SY5Y Cell Line

Bruk Getachew<sup>1</sup> · Antonei B. Csoka<sup>2</sup> · Allison R. Garden<sup>1</sup> · Robert L. Copeland<sup>1</sup> · Yousef Tizabi<sup>1</sup>

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## Abstract

Alcohol use disorder (AUD), brought about by excessive alcohol use, is associated with damages to several organs including the brain. Chronic excessive use of alcohol can compromise intestinal integrity, leading to changes in gut microbiota (GM) composition known as dysbiosis. Dysbiosis, by disruption of the gut-brain axis (GBA), further exacerbates the deleterious effects of alcohol. One of the fermentation by-products of GM is butyrate (BUT), a short-chain fatty acid (SCFA) that plays an important role in maintaining homeostasis of the GBA. Alcohol metabolism results in formation of acetaldehyde, a highly reactive compound that reacts with dopamine in the brain to form toxic adducts such as salsolinol. Recent studies indicate potential neuro-protective effects of BUT against various toxicants including salsolinol. Here, we sought to investigate whether BUT can also protect against alcohol toxicity. Pretreatment of neuroblastoma-derived SH-SY5Y cells with 500 mM ethanol (ETOH) for 24 h resulted in approximately 40% reduction in cell viability, which was totally blocked by 10 μM of either BUT or AR 420,626 (AR), a selective fatty acid 3 receptor (FA3R) agonist. The neuro-protective effects of both BUT and AR were significantly (80%) attenuated by beta-hydroxy butyrate (BHB), a selective FA3R antagonist. Interestingly, combination of BUT and AR resulted in synergistic protection against ETOH, which was totally blocked by BHB. These findings suggest potential utility of butyrate and/or FA3R agonists against ETOH-induced toxicity.

**Keywords** Alcohol · Butyrate · Short-chain fatty acids (SCFAs) · Gut microbiota · Fatty acid 3 receptor (FA3R) · Beta-hydroxy butyrate

## Introduction

Chronic excessive alcohol (CEA) use could lead to alcohol use disorder (AUD), a problematic pattern of alcohol use with an impaired ability to stop/control alcohol use despite adverse social, occupational, or health consequences (Koob 2021). CEA can cause neuronal loss by inducing neurotoxicity as well as inhibiting neurogenesis. This leads to significant volume loss in cortical and subcortical brain structures and shrinkage in both gray and white matters. These structural changes along with impairment in neuronal signaling and glial dysfunction result in short-term memory

loss and other behavioral abnormalities such as weakness, ataxia, motor speech disorder, diminished executive functioning, anxiety, and negative emotions (Tizabi et al. 2021b).

Recent development in the gut-brain axis (GBA) has confirmed a bidirectional and intimate cross talk between gut microbiome and the brain. Thus, the importance of normal intestinal colonization of the gut, starting at neonatal period and continuing throughout life, in critical physiological functions has been well established. Gut microbiome plays an essential role in food digestion, xenobiotic metabolism, and regulation of innate and adaptive immunological processes (Bishehsari et al. 2017; Cryan et al. 2019). Indeed, dysbiosis, a term representing a loss or reduction of beneficial bacteria and accumulation of pathogenic ones (Belizário and Faintuch 2018), has been associated with dysregulation of food intake and energy homeostasis (Romaní-Pérez et al. 2021; Woźniak et al. 2021) and implicated in a myriad of central nervous system (CNS) disorders such as anxiety and depression (Cryan et al. 2019; Knudsen et al. 2021; Poluektova et al. 2021),

✉ Yousef Tizabi  
ytizabi@howard.edu

<sup>1</sup> Department of Pharmacology, Howard University College of Medicine, 520 W Street NW, Washington, DC 20059, USA

<sup>2</sup> Department of Anatomy, Howard University College of Medicine, Washington, DC, USA

stroke (Yamashiro et al. 2021), multiple sclerosis (Ullah et al. 2021), Parkinson's disease (Tizabi et al. 2021a), autism (Kong et al. 2021), schizophrenia (Kelly et al. 2021), aging (Li et al. 2021; van Krimpen et al. 2021), cognitive dysfunction (Cryan et al. 2019; Cowan and Cryan 2021; Li et al. 2021), Alzheimer's disease (Giovannini et al. 2021; Jiang et al. 2021), and even substance abuse (Meckel and Kiraly 2019; García-Cabrerizo et al. 2021).

Dysbiosis due to alcohol abuse may be a contributing factor to AUD (Engen et al. 2015; Bishehsari et al. 2017). Thus, alcohol-induced changes in the gut microbiota may contribute not only to development of alcoholic liver disease, but also to a variety of CNS disorders (Engen et al. 2015; García-Cabrerizo et al. 2021). Indeed, it has been suggested that use of probiotic might be of potential use in prevention and treatment of alcohol-associated pathologies (Engen et al. 2015; Lowe et al. 2018; Rodriguez-Gonzalez and Orío 2020; Carbia et al. 2021; Gupta et al. 2021). In this regard, it was recently reported that butyrate (BUT) ameliorates alcoholic fatty liver disease in mice (Zhang et al. 2021).

Butyrate is a short-chain fatty acid (FA) that acts as an energy source for colonic epithelial cells. It has anti-inflammatory, enteroendocrine, and epigenetic effects and can also affect the brain function (Cantu-Jungles et al. 2019). The postulated mechanism of action of BUT includes its interaction with fatty acid receptor 3 (FA3R) which is a G protein coupled receptor, as well as inhibition of histone deacetylase (HDAC) (Cantu-Jungles et al. 2019; Falomir-Lockhart et al. 2019). Recently, our group reported protective effects of BUT against salsolinol-induced toxicity in neuroblastoma-derived SH-SY5Y cells (Getachew et al. 2020). The protective effects of BUT were mimicked by another FA3R agonist (AR), and both BUT and AR could be blocked by the FA3R antagonist, beta-hydroxy butyrate (BHB) (Kimura et al. 2011; Ulven 2012; Inoue et al. 2014; Getachew et al. 2020). Since salsolinol is produced via condensation of dopamine with aldehydes and was shown lately to be present in the ventral tegmental area of rats following oral alcohol administration (Bassareo et al. 2021), we undertook this study to determine whether BUT and/or AR could also protect against alcohol-induced toxicity in SH-SY5Y cells.

## Materials and Methods

Ethanol (ETOH, 100%) was obtained from EMD Chemicals Inc. (Gibbstown, NJ). Butyrate, beta-hydroxy butyrate (BHB), a selective FA3R antagonist (Kimura et al. 2011; Ulven 2012; Inoue et al. 2014), and other analytical reagents including 3,(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide (MTT) assay kit were purchased from Sigma Chemical Company (Sigma-Aldrich, St. Louis, MO). AR 420,626

(AR), chemical name: *N*-(2,5-dichlorophenyl)-4-(furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide, a FA3 receptor agonist (Hudson et al. 2014; Bolognini et al. 2016; Kaji et al. 2018), was purchased from Bio Techne Corp-Tocris (Minneapolis, MN). The SH-SY5Y human neuroblastoma cell line was purchased from American Type Culture Collection (ATCC, Manassas, VA).

As detailed previously (Getachew et al. 2018, 2020), SH-SY5Y cells were cultured in a 1:1 mixture of Dulbecco's modified Eagle's medium (DMEM) and Ham's F12 supplemented with 10% fetal bovine serum, penicillin/streptomycin (100 IU/ml), and gentamicin (50 µg/ml) at 37 °C in 95% O<sub>2</sub>/5% CO<sub>2</sub> humidified incubator. The cells (un-differentiated) were trypsinized when confluent and plated in 96-well plates (1.2 × 10<sup>4</sup> cells/well). Cells were allowed to adhere to bottom surface for 24 h. Then, fresh media containing ethanol (500 mM) or various concentrations of BUT or AR with and without FA3R antagonist were added to the carefully aspirated wells. The concentration of ethanol was chosen based on our previous experiments and the fact that such concentration results in approximately 40% toxicity in SH-SY5Y cells (Getachew et al. 2018). Butyrate or AR was added 1 h prior to ETOH, and FA3R antagonist, in turn, was added 1 h prior to BUT or AR. In combination studies, both BUT and AR were added simultaneously 1 h prior to ETOH. In all cases, the control group consisted of cells that were maintained in media alone and without any drug treatment. All treatments were carried out for 24 h, and the effects on cell viability were determined following the 24-h incubation. Each treatment group consisted of 6 replicates, and a minimum of 4 assays were conducted for each experimental manipulation.

Cell viability was determined by MTT colorimetric assay according to the manufacturer's protocol as described previously (Getachew et al. 2018, 2020). Briefly, the yellow MTT tetrazolium salt (0.5 mg/ml) was dissolved in phosphate-buffered saline (PBS) with 10 mM (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES). Thirty microliters of MTT was added to each well and incubated for 3 h at 37 °C. The live cells cause a reduction of the yellow salt to insoluble purple formazan crystals. The wells were then carefully aspirated, and 50 µl of dimethyl sulfoxide (DMSO) was added to the wells to solubilize the crystals; the plates were then placed in a shaker for an hour and read spectrophotometrically at 570 nm with a background of 630 nm in a plate reader. Cell viability was determined by subtracting the test results from the background and is presented as a percentage of the control.

Data is expressed as mean ± standard error of the mean (SEM). Statistical differences within and between treatment groups were determined by one-way analysis of variance (ANOVA) followed by post hoc Newman-Keuls Multiple comparison test, where *p* < 0.05 was considered statistically

significant. Data were analyzed using GraphPad Prism 9.2 (GraphPad Software, Inc., San Diego, CA).

## Results

Figure 1 depicts the effect of various concentrations of BUT (0.01–10  $\mu\text{M}$ ) against ETOH-induced toxicity in SH-SY5Y cells. For ETOH, we used a concentration of 500 mM because we have consistently observed about 40% toxicity during the 24-h exposure with this concentration (Getachew et al. 2018). As seen, there was a concentration-dependent protection by BUT against ETOH toxicity with full protection at 10  $\mu\text{M}$  [ $F(5,24) = 14.8, p < 0.01$ ]. Butyrate by itself, at any concentration, did not affect the cell viability (data not shown).

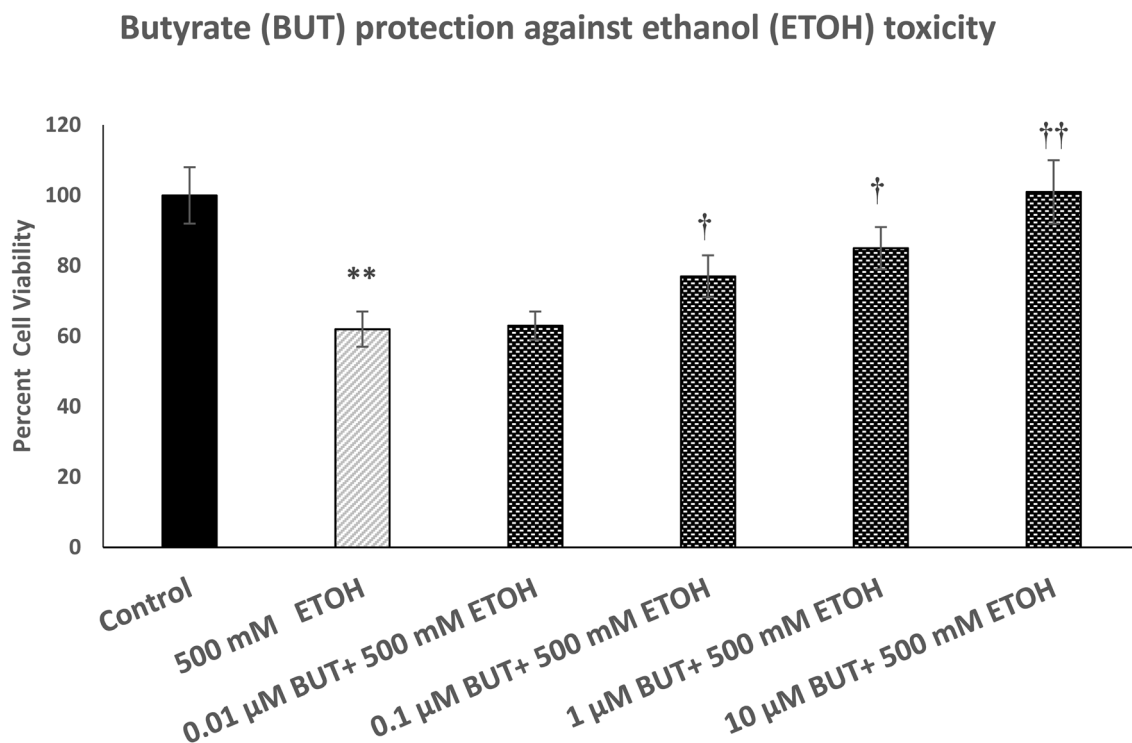
Figure 2 depicts the effect of various concentrations of AR (0.01–10  $\mu\text{M}$ ) against ETOH-induced toxicity. Here also, there was a concentration-dependent protection by AR against ETOH-induced toxicity. Full protection was achieved at 10  $\mu\text{M}$  AR [ $F(5,24) = 13.6, p < 0.01$ ]. AR by itself, at any concentration, did not affect the cell viability (data not shown).

Figure 3 depicts the effect of various concentrations of FA3R antagonist (BHB) on protective effects of BUT

against ETOH-induced toxicity. We used the highest concentration of BUT (10  $\mu\text{M}$ ) as this concentration was fully protective against ETOH toxicity. As seen, there was a concentration-dependent attenuation of BUT effect by BHB [ $F(7,32) = 16.4, p < 0.01$ ]. The highest concentration of BHB (60  $\mu\text{M}$ ) reduced the protective effects of BUT by approximately 80% ( $p < 0.01$ ). BHB did not have any effect of its own on cell viability at any of the concentrations used (data not shown). We did not try any higher BHB concentration, because at 80  $\mu\text{M}$ , it caused some of its own toxicity.

Figure 4 depicts the effect of various concentrations of BHB on protective effects of AR against ETOH-induced toxicity. We used the highest concentration of AR (10  $\mu\text{M}$ ) as this concentration was fully protective against ETOH-induced toxicity. As shown, there was a concentration-dependent attenuation of AR protection by BHB [ $F(7,32) = 14.5, p < 0.01$ ]. In this case also, the highest concentration of BHB (60  $\mu\text{M}$ ) reduced the protective effects of AR by approximately 80% ( $p < 0.01$ ).

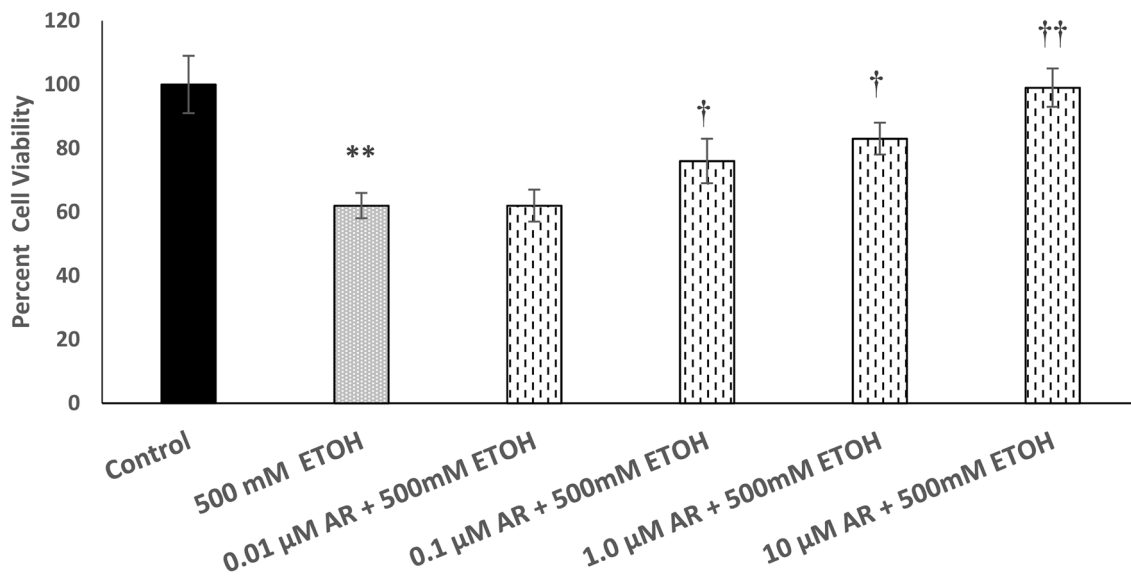
Figure 5 depicts the effect of combination of low concentrations of BUT and AR. Whereas neither butyrate nor AR at 0.01  $\mu\text{M}$  concentration had any protective effect against ETOH toxicity, the combination of the two resulted in approximately 50% protection [ $F(9,42) = 12.1, (p < 0.01)$ ]. The combination of 0.1  $\mu\text{M}$  BUT and 0.1  $\mu\text{M}$  AR, where



**Fig. 1** Effect of various concentrations of butyrate (BUT) against ethanol (ETOH)-induced toxicity. Cells were treated with ETOH with and without BUT for 24 h, and cell viability was determined by

MTT. BUT was added 1 h before ETOH. Values are mean  $\pm$  SEM. \*\* $p < 0.01$  compared to control, † $p < 0.05$ , †† $p < 0.01$  compared to ETOH.  $N = 4$  per treatment

### AR protection against ethanol (ETOH) toxicity



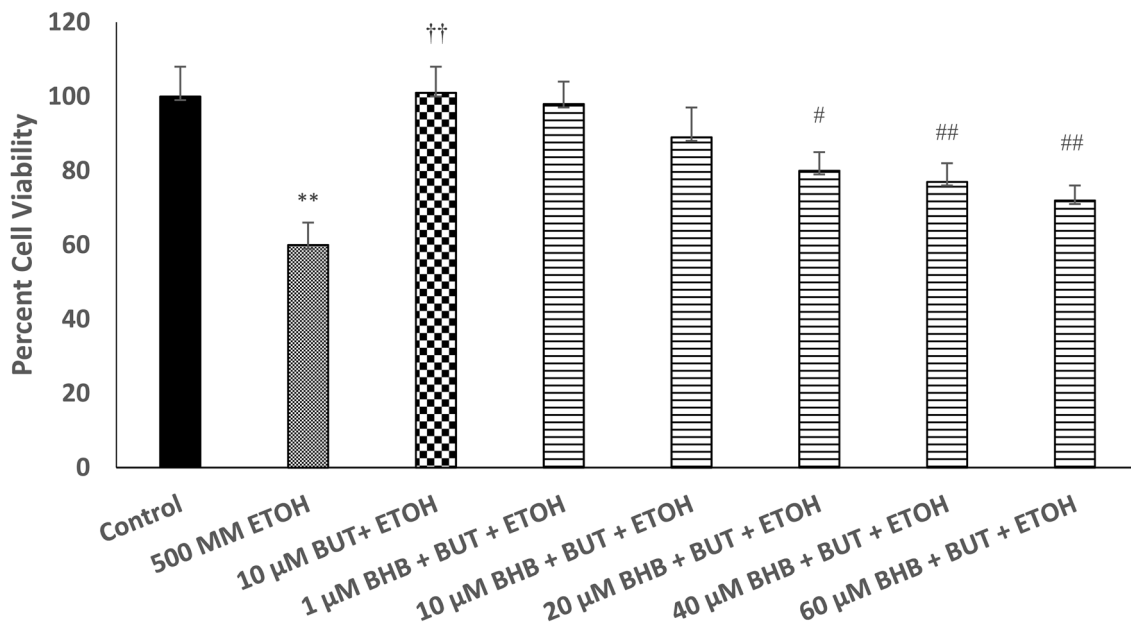
**Fig. 2** Effect of various concentrations of AR, a selective FA3R agonist, against ethanol (ETOH)-induced toxicity. Cells were treated with ETOH with and without AR for 24 h, and cell viability was determined by MTT.

AR was added 1 h before ETOH. Values are mean ± SEM. \*\* $p < 0.01$  compared to control, † $p < 0.05$ , †† $p < 0.01$  compared to ETOH.  $N = 4$  per treatment

each had approximately 24% protection, resulted in complete protection against ETOH [ $F(9,42) = 12.1$ , ( $p < 0.01$ )]. Moreover, the effects of the combination treatments at

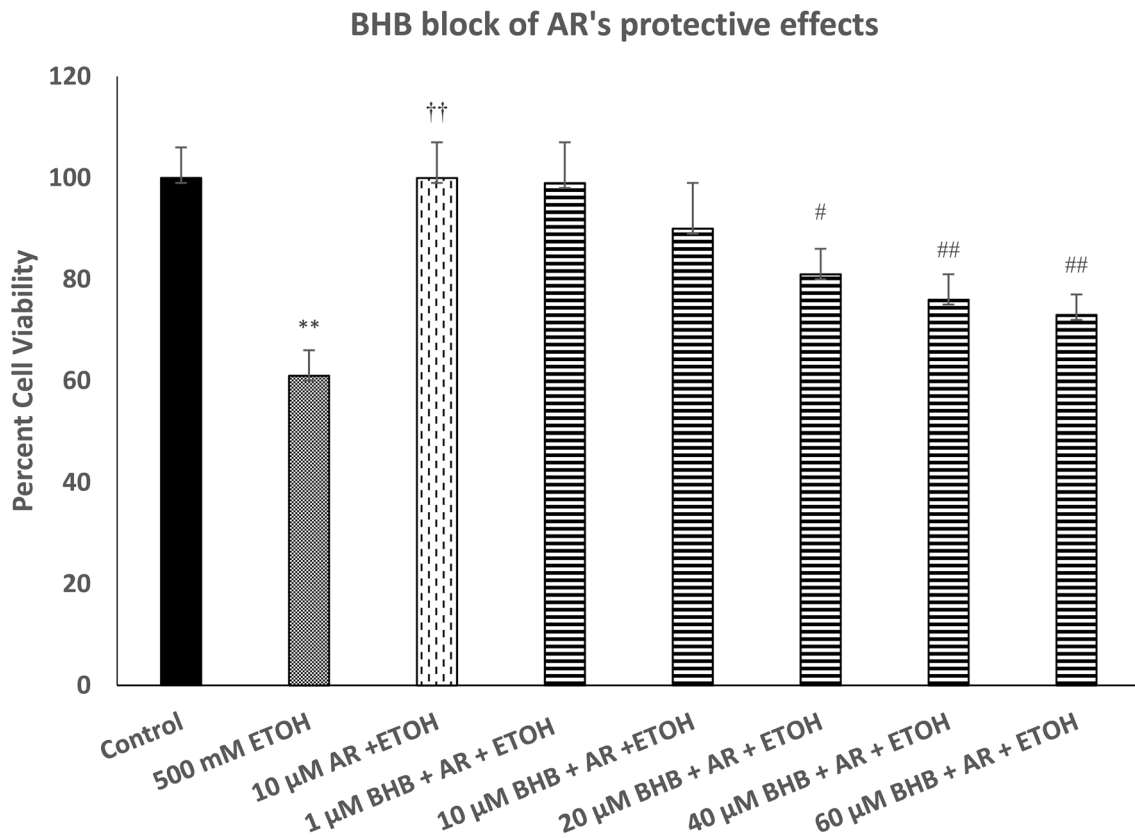
either concentration levels were totally blocked with the highest concentration of BHB (60 μM) [ $F(9,42) = 12.1$ , ( $p < 0.01$ )].

### BHB block of BUT's protective effects



**Fig. 3** Effect of various concentrations of beta-hydroxy butyrate (BHB), a FA3R antagonist, on protective effects of butyrate (BUT) against ethanol (ETOH)-induced toxicity. Cells were treated with ETOH, BUT, and BHB for 24 h and cell viability was determined

by MTT. BHB was added 1 h before BUT, which was added 1 h before ETOH. Values are mean ± SEM. \*\* $p < 0.01$  compared to control. †† $p < 0.01$  compared to ETOH, # $p < 0.05$ , ## $p < 0.01$  compared to BUT + ETOH.  $N = 4$  per treatment



**Fig. 4** Effect of various concentrations of beta-hydroxy butyrate (BHB), a FA3R antagonist, on protective effects of AR against ethanol (ETOH)-induced toxicity. Cells were treated with ETOH, AR, and BHB for 24 h, and cell viability was determined by MTT. BHB

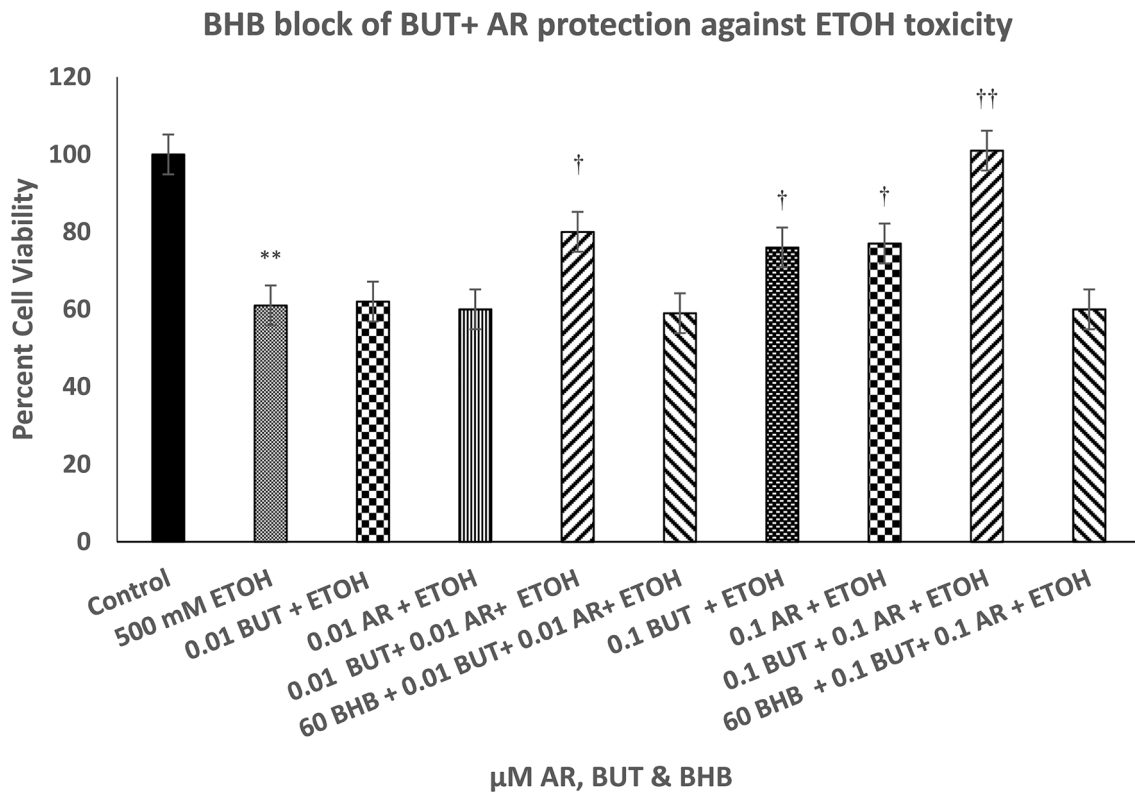
was added 1 h before AR, which was added 1 h before ETOH. Values are mean  $\pm$  SEM. \*\* $p < 0.01$  compared to control. †† $p < 0.01$  compared to ETOH, # $p < 0.05$ , ## $p < 0.01$  compared to AR + ETOH.  $N = 4$  per treatment

## Discussion

The results of this study show that BUT as well as AR, an FA3R agonist, can protect against ETOH-induced toxicity in neuroblastoma-derived dopaminergic cells. Moreover, a synergistic protective effect of low concentrations of BUT and AR was also observed. Thus, a combination of ineffective or very low concentrations of BUT and AR resulted in more than an additive protection against ETOH toxicity. Pre-treatment of cells with BHB, a selective FA3R antagonist, substantially reduced the protective effects of BUT and AR individually and completely blocked the protective effects of the combined concentrations of the two drugs. These results support potential beneficial effects of BUT and/or an FA3R agonist in alcohol toxicity.

The findings also extend the utility of short-chain fatty acids (SCFAs) beyond the neurodegenerative diseases such as Parkinson's disease (PD), to a common toxicant such as alcohol. Although further *in vivo* studies are required to validate this premise in relation to alcohol, such observations have been reported in PD models (St Laurent et al. 2013; Liu et al. 2017). Interestingly, in regard to cellular model of

PD, protective effects of BUT against salsolinol were also partially blocked by BHB, whereas the protective effects of AR against salsolinol were fully blocked by BHB (Getachew et al. 2020). Since AR is considered a full FA3R agonist (Hudson et al. 2014; Bolognini et al. 2016; Kaji et al. 2018) and BHB a selective FA3R antagonist (Kimura et al. 2011; Ulven 2012; Inoue et al. 2014), it was suggested that protective effects of BUT against salsolinol may involve more than FA3R activation (Getachew et al. 2020). This may include HDAC inhibition, activation of Nrf2/HO-1 axis, and stimulation of glucagon like peptide-1 (Funakoshi-Tago et al. 2018; Liu et al. 2017; Cantu-Jungles et al. 2019). Although it remains to be determined whether AR also shares any of such BUT characteristics, the finding that BHB could only partially block the protective effects of either BUT or AR against ETOH may also indicate involvement of other mechanism(s) in protection by BUT and AR against ETOH toxicity. However, the finding that the synergistic effects of the combination of BUT and AR could be fully blocked by BHB suggests that adequate activation of the FA3R might be sufficient for observed protection against ETOH toxicity and that the efficacy or potency of BHB to block FA3R might be limited.



**Fig. 5** Effect of beta-hydroxy butyrate (BHB), a FA3R antagonist, on protective effects of the combination of butyrate (BUT) and AR against ethanol (ETOH)-induced toxicity. Cells were treated with ETOH, BUT+AR, and BHB for 24 h, and cell viability was deter-

mined by MTT. BHB was added 1 h before BUT+AR, which was added 1 h before ETOH. Values are mean  $\pm$  SEM. \*\* $p < 0.01$  compared to control. † $p < 0.5$ , †† $p < 0.01$  compared to ETOH.  $N = 4-5$  per treatment

SCFAs in general and BUT in particular may not only prevent neurotoxicity induced by such compounds as sal-solinol or ETOH but may also be of potential utility in other diseases such as graft rejection, inflammatory bowel disease, colorectal cancer, and diabetes, all of which carry an inflammatory component (Tikhonova 2017; Alrafas et al. 2019; Baxter et al. 2019). As mentioned earlier, anti-inflammatory effects of BUT are well established (Cantu-Jungles et al. 2019). Interestingly, BUT may also be of therapeutic potential in both alcoholic- and non-alcoholic fatty liver diseases (Ralli et al. 2021; Zhang et al. 2021). In addition, BUT has been advocated for treatment of obesity and sleep disorders (Baxter et al. 2019; Szentirmai et al. 2019) and most recently for control of cytokine storm associated with COVID-19 (Nithin et al. 2021). However, because BUT has short half-life due to first-pass hepatic clearance (Miller et al. 1987; Kumar et al. 2019; Dingeo et al. 2020), AR, or any selective FA3R agonist, with a better pharmacologic profile than BUT, may offer a desirable alternative.

In summary, the findings support the potential use of butyrate and/or a selective FA3R agonist in combating alcohol toxicity.

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## Declarations

**Conflict of Interest** The authors declare no competing interests.

**Disclaimers** The authors indicate that the views expressed in the submitted article are their own and not an official position of the institution or the funding agency.

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