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Butyrate protects against salsolinol-induced toxicity in SH-SY5Y cells: implication for Parkinson's disease

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Abstract

Parkinson's disease (PD), a progressive neurodegenerative disorder, is associated with the destruction of dopamine neurons in the substantia nigra (SN) and the formation of Lewy bodies in basal ganglia. Risk factors for PD include aging, as well as environmental and genetic factors. Recent converging reports suggest a role for the gut microbiome and epigenetic factors in the onset and/or progression of PD. Of particular relevance and potential therapeutic targets in this regard, are histone deacetylases (HDACs), enzymes that are involved in chromatin remodeling. Butyrate, a short-chain fatty acid (FA) produced in the gut and presumably acting via several G protein-coupled receptors (GPCRs) including FA3 receptors (FA3Rs), is a well-known HDAC inhibitor that plays an important role in maintaining homeostasis of the gut-brain axis. Recently, its significance in regulation of some critical brain functions and usefulness in neurodegenerative diseases such as PD has been suggested. In this study we sought to determine whether butyrate may have protective effects against salsolionl (SALS)-induced toxicity in SH-SY5Y cells. SALS, an endogenous product of aldehyde and dopamine condensation, may be selectively toxic to dopaminergic neurons. SH-SY5Y cells, derived from human neuroblastoma cells are used as a model of these neurons. Exposure of SH-SY5Y cells for 24 h to 400 μM SALS resulted in approximately 60% cell death, which was concentration-dependently prevented by butyrate. The effects of butyrate in turn, were significantly attenuated by beta-hydroxy butyrate (BHB), a selective FA3R antagonist. Moreover, a selective FA3R agonist (AR 420626) also provided protective effects against SALS, which was totally blocked by BHB. These findings provide further support that butyrate or an agonist of FA3R may be of therapeutic potential in PD.

Keywords

Butyrate; Free Fatty Acid; FA3 Receptor; AR 420626; Parkinson's Disease; Neurodegeneration; SH-SY5Y Cells

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Introduction

The search for slowing or stopping the progression of the devastating neurodegenerative diseases in general, and Parkinson's disease (PD) in particular, is an ongoing challenge as the etiology of these diseases remain elusive. Moreover, the complexity of neurocircuitries make it unrealistic to assume that targeting a single neurotransmitter and/or receptor may provide the sought-after "silver bullet." However, recent advances in our understanding of the gut-brain axis and the epigenetic influences on brain function, offer new insights and potential novel targets for therapeutic intervention in PD. It is now believed that the initiation and progression of PD may be impeded through manipulation of the gut microbiota (Sampson et al. 2016: Sun and Shen 2018; Abdel-Haq et al. 2019). Specifically, it is suggested that dysbiosis or altered colonic microbiota can lead to neuroinflammation and misfolding of alpha-synuclein (α-Syn), a protein highly implicated in PD pathology (Keshavarzian et al. 2015; Sampson et al. 2016; Yang et al. 2019; Baizabal-Carvallo and Alonso-Juarez 2020). Furthermore, it has been reported that the composition of the gut microbiota and the short chain fatty acids (SCFAs) differ between patients with PD and age-matched controls (Unger et al. 2016: Sun and Shen 2018; Baizabal-Carvallo and Alonso-Juarez 2020).

Butyrate, a short chain FA, acting as an energy source for colonic epithelial cells, has anti-inflammatory, enteroendocrine and epigenetic effects that not only can influence colonic and systemic health, but can also affect the brain function (Cantu-Jungles et al. 2019). Indeed, a few studies indicate beneficial effects of butyrate in animal models of PD (Laurent et al. 2013; Liu et al. 2017). Although the exact mechanism of action of butyrate in the central nervous system remains far from complete, it is known to interact with fatty acid receptor 3 (FA3R), which is a G protein coupled receptor. FA3R also known as GPR41, and FA2R also known as GPR43, are related members of a homologous family of orphan G protein-coupled receptors that are tandemly encoded at a single chromosomal locus in both humans and mice. Moreover, GPR41 is related to GPR43 (52% similarity; 43% identity) and are activated by similar ligands but with differing specificity. Thus, acetate preferentially activates FA2R, whereas butyrate preferentially activates FA3R, which is also the one predominantly expressed in enteric neurons of the submucosal and myenteric ganglia, and in several of the postganglionic sympathetic and sensory neurons, both in autonomic and somatic peripheral nervous system (Brown et al. 2003; de Clercq et al. 2016; Kaji et al. 2018; Falomir-Lockhart et al. 2019).

It is well known that PD, characterized by movement disorders, is the result of damage or destruction of dopaminergic neurons in the substantia nigra. Although, as eluded earlier, the causes of PD are unknown, some atypical cases seem to have a genetic origin. However, these familial cases account for a rather small percentage of incidences as the majority of cases are sporadic and hence, of unknown etiology (Healy et al. 2004; Morris, 2005; Tizabi et al. 2019). Recent advances in PD pathology suggest that the neuronal degeneration in this disease likely involves several cellular and molecular events including: proapoptotic mechanisms, oxidative stress and microglia-mediated inflammation (Hurley and Tizabi 2013; Maiti et al. 2017; Reglodi et al. 2017; Ho 2019) as well as gut microbial dysbiosis (Sampson et al. 2016; Yang et al. 2019; Baizabal-Carvallo and Alonso-Juarez 2020).

SH-SY5Y cells, human neuroblastoma-derived cells, express high levels of dopaminergic activity and are used extensively as a cellular model to study mechanism(s) of toxicity and protection in nigral dopaminergic neurons (Storch et al. 2002; Maruyama et al. 2004; Naoi et al. 2004; Copeland et al. 2007; Kovalevich and Langford, 2013). Salsolinol (SALS), an endogenous neuromodulator in dopaminergic cells, is formed during the metabolism of dopamine and is the condensation product of dopamine and aldehydes (Mravec, 2006). Dysregulation of SALS, especially its (R) enantiomer in the brain, is thought to contribute to the pathogenesis of idiopathic of PD (Antkiewicz-Michaluk, 2002; Xicoy et al. 2017; Kurnik-Łucka et al. 2018). Because of its selective toxicity to dopaminergic cells, we and others have used SALS-induced toxicity in SH-SY5Y cells to screen potential neuroprotectants, specifically applicable to PD (Copeland et al. 2007; Qualls et al. 2014; Xicoy et al. 2017; Getachew et al. 2019).

In this study, using the SH-SY5Y cell line, we investigated potential protection of butyrate against SALS-induced toxicity as well as possible involvement of FA3Rs in butyrate's action.

Materials and Methods

Butyrate, beta-hydroxy butyrate (BHB), a selective FA3R antagonist (Kimura et al. 2011; Ulven 2012; Inoue et al. 2014), SALS, 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 420626 (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 purchase form Bio Techne Corp-Tocris (Minneapolis, MN). The SH-SY5Y human neuroblastoma cell line was purchased from American Type Culture Collection (ATCC, Manassas, VA).

As reported in detail previously (Manavalan et al. 2017; Getachew et al. 2018, 2019), SH-SY5Y cells were cultured in a 1:1 mixture of Dulbeccos Modified Eagle Medium (DMEM) and Ham's F12 supplemented with 10 % fetal bovine serum, penicillin/streptomycin (100 IU/ml), and gentamicin (50ug/ml) at 37° C in 95% O_2/5% CO_2 humidified incubator. The cells (un-differentiated) were trypsinized when confluent and plated in 96 well plates (1.2×10^4 cells/well). Cells were allowed to adhere to bottom surface for 24 h. Then, fresh media containing SALS (400 μM) or various concentrations of butyrate or AR with and without butyrate antagonist were added to the carefully aspirated wells. Butyrate or AR were added one hour prior to SALS and butyrate antagonist, in term was added one hour prior to butyrate or AR. 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 cell viability study was run in sextuplicate (i.e., 6 replicates) and a minimum of 4 assays were conducted for each experimental manipulation.

Determination of cell viability was done by MTT colorimetric assay according to the manufacturer's protocol as described previously (Manavalan et al. 2017; Getachew et al.

2018, 2019). 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). 30 μl 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 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 6 (Graphpad Software, Inc., San Diego, CA).

Results

Figure 1 depicts the effect of various concentrations of butyrate (0.01 – 20 μM) against SALS-induced toxicity in SH-SY5Y cells. For SALS, we used a concentration of 400 μM because we have consistently observed over 60% toxicity during the 24 h exposure with this concentration (Copeland et al. 2007; Getachew et al. 2018, 2019). As seen, there was a concentration-dependent protection by butyrate against SALS toxicity with full protection at 20 μM butyrate [$F(4,20)=15.2$, $p<0.01$]. 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 – 20 μM) against SALS-induced toxicity. Here also, there was a concentration-dependent protection by AR against SALS-induced toxicity. Full protection was achieved at 20 μM AR [$F(4,20)=14.1$, $p<0.01$]. AR by itself, at any concentration, did not affect the cell viability (data not shown).

Figure 3 depicts effect of various concentrations of FA3R antagonist (BHB) on protective effects of butyrate against SALS-induced toxicity. We used the highest concentration of butyrate (20 μM) as this concentration was fully protective against SALS toxicity. As seen, there was concentration-dependent attenuation of butyrate effect by BHB [$F(4,20)=18.8$, $p<0.01$]. The highest concentration of BHB (60 μM) reduced the protective effects of butyrate by approximately 40% ($p<0.01$). BHB did not have any effect of its own on cell viability at any of the concentrations used (data not shown).

Figure 4 depicts effect of various concentrations of BHB on protective effects of AR against SALS-induced toxicity. We used the highest concentration of AR (20 μM) as this concentration was fully protective against SALS-induced toxicity. As seen, there was a concentration-dependent attenuation of AR protection by BHB [$F(4,20)=13.6$, $p<0.01$]. In this case, however, the highest concentration of BHB (60 μM) fully blocked the effects of AR ($p<0.01$).

Discussion

The results of this study show for the first time that butyrate as well as AR, an FA3R agonist can protect against salsolinol-induced toxicity in neuroblastoma-derived dopaminergic cells. Moreover, partial effect of BUT, and whole effect of AR could be blocked by BHB, a selective FA3R antagonist. These findings support potential therapeutic efficacy of butyrate or an FA3R agonist in PD.

Although the etiology of sporadic PD remains to be fully understood, substantial evidence implicates dysbiosis or disturbance in gut microbiota as an important contributor to its pathophysiology (Sampson et al. 2016: Sun and Shen 2018; Abdel-Haq et al. 2019; Cantu-Jungles et al. 2019; Baizabal-Carvallo and Alonso-Juarez 2020). Indeed, it has been reported that PD is associated with hyperpermeability of the colonic epithelium (Forsyth et al. 2011). Moreover, as indicated above dysbiosis or altered colonic microbiota can lead to neuroinflammation and misfolding of α-Syn, a protein highly implicated in PD pathology (Keshavarzian et al. 2015). Several microbiota have been associated with PD. Thus, lower abundance of *Lachnospiraceae* family members and *Faecalibacterium* as well as low production of several SCFAs including butyrate, have been observed in patients with PD (Cantu-Jungles et al. 2019). Interestingly, administration of butyrate can shift the balance of gut flora in favor of beneficial microbiota and hence normalization of dysbiosis (Zhou et al. 2017). Moreover, beneficial effects of butyrate in animal models of PD have been reported (Laurent et al. 2013; Liu et al. 2017).

Although several SCFAs with significant importance in maintaining the colonic epithelial cells exist, butyrate has attracted particular interest not only due to its beneficial effects on cellular metabolism, but also because of its role in modulating immune and inflammatory responses as well as its potential usefulness in neurodegenerative diseases (Laurent et al 2013; Liu et al. 2018, Cantu-Jungles et al. 2019). Several mechanisms have been implicated in butyrate's action. These include acting as an HDAC inhibitor, activation of Nrf2/HO-1 axis, stimulation of glucagon like peptide-1 and binding to several specific G protein–coupled receptors (GPCRs) such as FA2R and FA3R (Funakohi-Tago et al. 2018; Liu et al. 2017, Cantu-Jungles et al. 2019). In terms of the latter effect, it is noteworthy that butyrate preferentially activates FA3R, which is primarily expressed on neuronal cells including enteric, sympathetic and sensory neurons (Nøhr et al. 2013; Tough et al. 2018; Falomir-Lockhart et al, 2019).

Since BHB, a selective FA3R antagonist, only partially blocked the protective effects of butyrate, it may be concluded that other mechanism(s), in addition to its activation of FA3R are involved in butyrate's neuroprotective effects. Interestingly, non-FA3R mediated effects of butyrate have also been observed in other conditions, for example, protection against diet-induced obesity (Lin et al. 2012). However, the fact that AR, a selective FA3R agonist can also exert protective effects against SALS indicates that activation of this receptor alone might be sufficient to induce neuroprotection, particularly of relevance to PD. This contention is based on the results where BHB, a selective FA3R antagonist can totally block the protective effects of AR.

Beneficial effects of butyrate in PD are further evidenced by its attenuation of motor impairments induced by 6-hydroxydopamine, rotenone or MPTP in rat models of PD (Srivastav et al. 2019). In addition, butyrate may confer neuroprotection against dopamine cell death, DNA damage, oxidative stress and protein aggregation induced by lipopolysaccharide (LPS), via HDAC inhibition (Srivastav et al. 2019). It is of relevance to note that Sampson et al (2016), using mice overexpressing αSyn and germ-free mice, which are devoid of gut microbiota, conclude that gut microbiota is required for motor deficits, microglia activation, and αSyn pathology. However, in the same study they also report that colonization of αSyn-overexpressing mice with microbiota from PD patients enhances physical impairments compared to microbiota transplants from healthy human donors, thus, strongly suggesting that abnormality in the gut bacteria transferred from PD patients contribute to movement disorders in mice (Sampson et al. 2016). Collectively, abundance of reports indicate beneficial effects of SCFA in general and butyrate in particular (Lanza et al., 2019; Srivastav et al 2019; Nuzum et al 2020).

In addition, it is now well recognized that butyrate not only may have neuroprotective effects but may also offer protection against several other diseases including graft rejection, inflammatory bowel disease, colorectal cancer and diabetes, all of which carry an inflammatory component (Tikhonova 2017; Alrafas et al. 2019; Nielson et al. 2019). In addition, butyrate was recently advocated for treatment of obesity and sleep disorders (Nielson et al. 2019; Szentirmai et al. 2019). However, butyrate's poor pharmacologic properties such as short half-life and first-pass hepatic clearance pose some limitation on its therapeutic efficacy (Witt et al. 2003; Sampathkumar et al. 2006; Yoo and Jones, 2006; Ghosh et al. 2012). Therefore, it would be of significant interest to determine whether AR or any selective FA3R agonist, with a better pharmacologic profile than butyrate, may also have similar protection in myriad of diseases affected by butyrate. In this regard it was recently reported that selective FA3 agonist may be a potential therapeutic candidate for NSAID-induced enteropathy (Said et al. 2017).

In summary, the findings support the potential use of butyrate or a selective FA3R agonist in PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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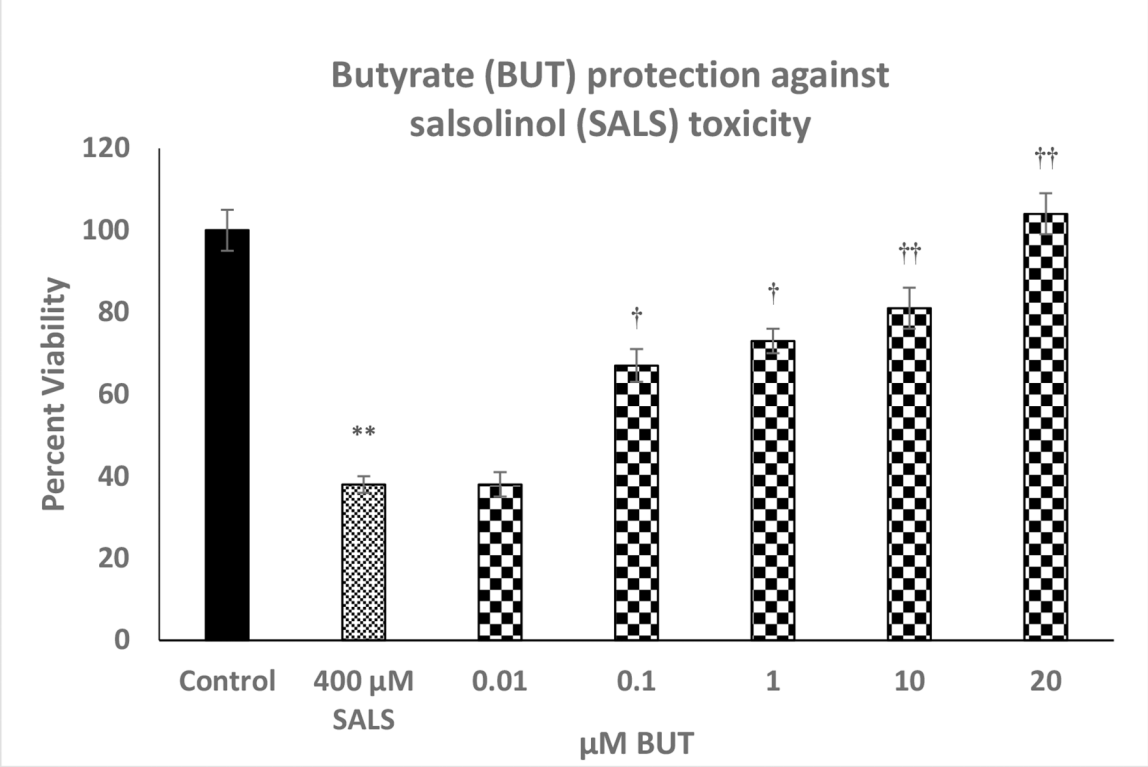

Fig. 1.

Effect of various concentrations of butyrate (BUT) against salsolinol (SALS)-induced toxicity. Cells were treated with SALS with and without BUT for 24 h and cell viability was determined by MTT. BUT was added 1 h before SALS. Values are mean ± SEM. *p<0.05, **p<0.01 compared to control. N = 5 per treatment

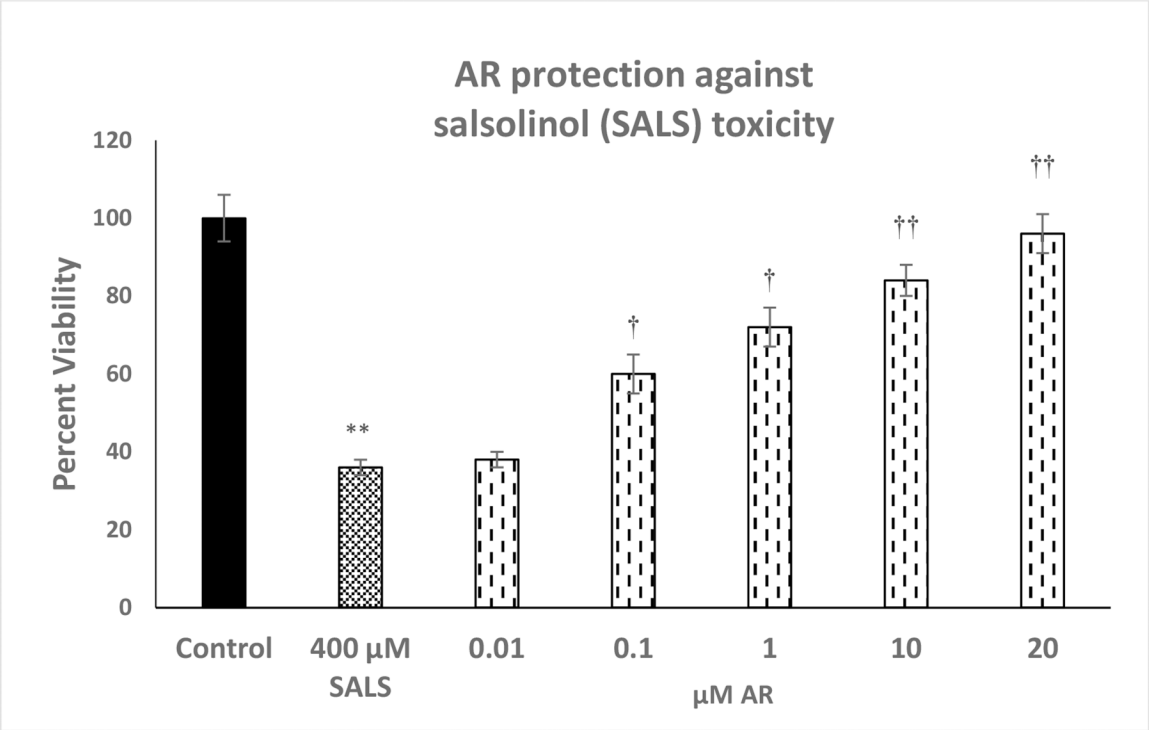

Fig. 2.

Effect of various concentrations of AR, a selective FA3R agonist, against salsolinol (SALS)-induced toxicity. Cells were treated with SALS with and without AR for 24 h and cell viability was determined by MTT. AR was added 1 h before SALS. Values are mean ± SEM. *p<0.05, **p<0.01 compared to control. N = 5 per treatment

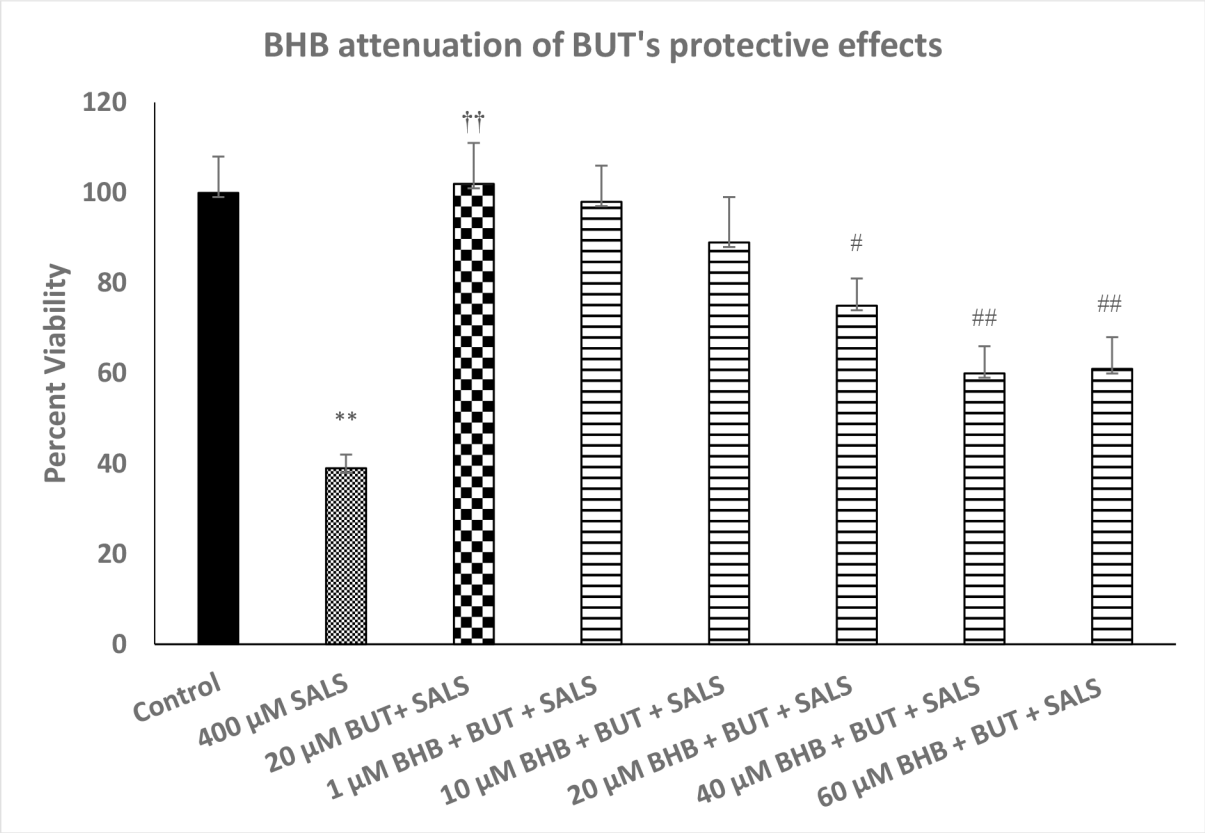

Fig. 3.

Effect of various concentrations of beta-hydroxy butyrate (BHB), a FA3R antagonist, on protective effects of butyrate (BUT) against salsilinol (SALS)-induced toxicity. Cells were treated with SALS, 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 SALS. Values are mean ± SEM. **$p<0.01$ compared to control. $^{††}p<0.01$ compared to SALS, $^{#}p<0.05$, $^{##}p<0.01$ compared to BUT + SALS. N = 4–5 per treatment

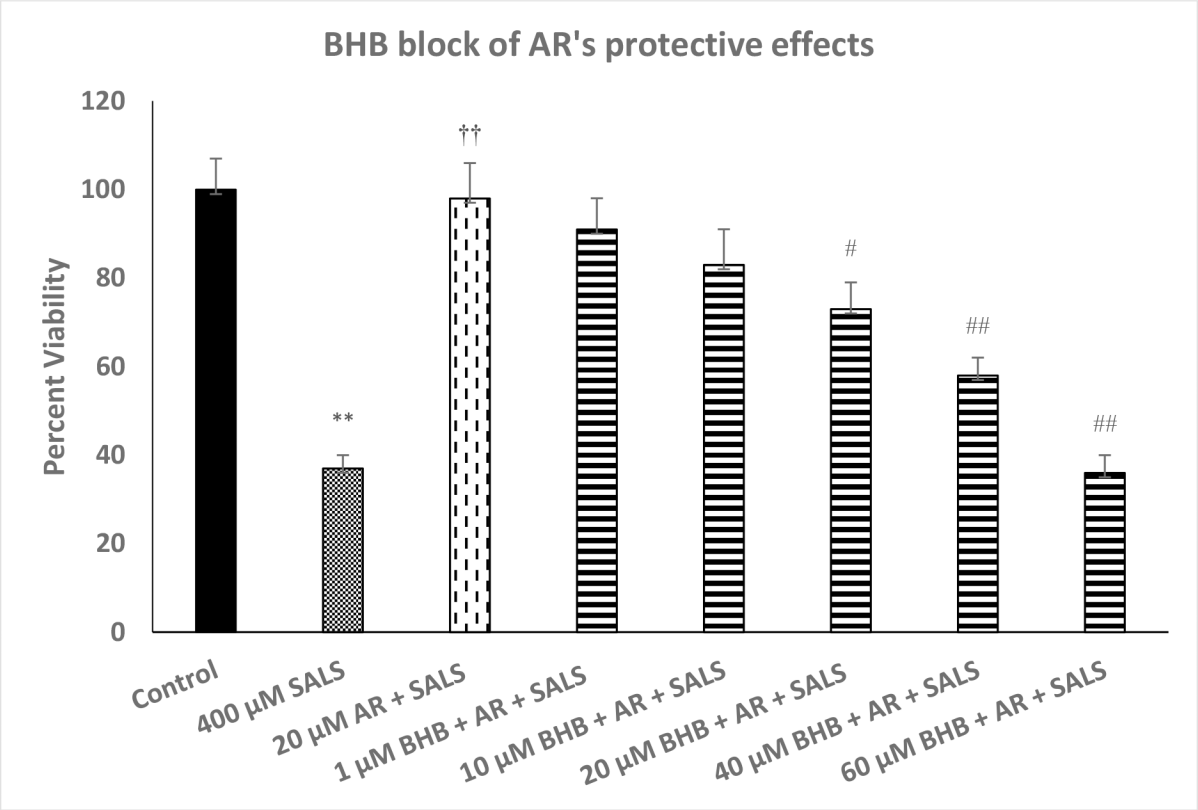

Fig. 4.

Effect of various concentrations of beta-hydroxy butyrate (BHB), a FA3R antagonist, on protective effects of AR against salsilino (SALS) iduced toxicity. Cells were treated with SALS, 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 SALS. Values are mean ± SEM. **p<0.01 compared to control. ††p<0.01 compared to SALS, #p<0.05, ##p<0.01 compared to AR + SALS. N = 4–5 per treatment