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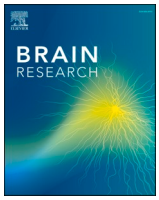

Research paper

Cutamesine attenuates hippocampal damage via sigma-1 receptor activation following oxygen-glucose deprivation *in vitro*

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ABSTRACT

Cerebral ischemia is a leading cause of death and disability worldwide, due to neuronal energy failure, calcium overload, ER stress and inflammation. Sigma-1 receptor activation regulates calcium signaling between ER and mitochondria and reduces the activation of ER stress and inflammation pathways.

In the present study, we investigated the neuroprotective effects of the sigma-1 receptor agonist cutamesine in rat organotypic, and acute hippocampal slices exposed to oxygen-glucose deprivation (OGD), two *in vitro* models of global ischemia. In organotypic hippocampal slices obtained from both sexes exposed to 30 min of OGD, we evaluated the neuroprotective effects of cutamesine by quantifying CA1 cell death via propidium iodide fluorescence. We also assessed mRNA and protein levels of key ER stress and inflammation markers via RT-qPCR and Western blot. In acute hippocampal slices, we evaluated the effects of cutamesine on recorded extracellular field excitatory postsynaptic potentials following OGD.

Cutamesine exhibited neuroprotective effects at 10 μg/mL in organotypic hippocampal slices exposed to 30 min of OGD, and this effect was reduced by the sigma-1 receptor antagonist BD1047. Cutamesine reduced ER stress and inflammation pathways by decreasing GRP78, GRP94, p-p65, and MMP-9 protein levels and these effects were partially decreased by BD1047. Cutamesine also delayed the onset of anoxic depolarization latency on acute hippocampal slices obtained from male rats. These findings evidence the notion that the sigma-1 receptor may be a promising therapeutic target for ischemic injury.

Abbreviations: aCSF, artificial cerebrospinal fluid; AD, anoxic depolarization; Cornu Ammonis 1, CA1; ER, endoplasmic reticulum; fEPSP, field excitatory postsynaptic potentials; GRP78, 78-kDa glucose-regulated protein; GRP94, glucose-regulated protein 94; IL-1β, interleukin-1 beta; MAMs, mitochondria-associated membranes; MMP-9, matrix metalloproteinase-9; OGD, oxygen and glucose deprivation; PI, propidium iodide; p-NF-κB, phosphorilated nuclear factor -kappa-B p65 subunit (p-p65); ROS, reactive oxygen species; Sig-1 receptor, sigma-1 receptor; TNF-α, tumor necrosis factor-alpha; UPR, unfolded protein response.

1. Introduction

Cerebrovascular diseases are among the primary causes of death and disability, according to the Global Burden of Disease. (Wang et al., 2024). Cerebral ischemia is caused by a transient or permanent reduction in cerebral blood flow, leading to insufficient oxygen and glucose in the brain cells and ultimately causing neuronal death and neurodegeneration (Campbell et al., 2019). The excessive glutamate release that follows an ischemic insult, causes N-methyl-D-aspartate receptor overactivation, and subsequently intracellular calcium overload in affected neurons. This condition initiates the so-called ischemic cascade characterized by reduction of calcium reuptake by the endoplasmic

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reticulum (ER) resulting in intracellular calcium overload, which disrupts mitochondrial activity and enhances inflammation via induction of pro-inflammatory cytokines release (Ludhiadch et al., 2021). In addition, brain ischemia triggers unfolded proteins accumulation (ER stress), primarily due to mitochondrial impairment. This combination of disrupted homeostasis, calcium overload, and ER stress can ultimately lead to neuronal cell death. (Mehta, 2014; Ren et al., 2021).

Sigma-1 receptors (Sig-1 receptor) are primarily located in the ER and are closely associated with mitochondria at specialized contact points called mitochondria-associated membranes (MAMs) (Linciano et al., 2023). They are crucial for the regulation of the ER-mitochondria calcium crosstalk, ion channels and neurotransmitter release, as well as inflammation, neuroprotection and cell survival in response to ischemic stress (Hayashi and Su, 2007; Tsai et al., 2015; Wang et al., 2023). Cutamesine (SA4503), a selective Sig-1 receptor agonist, binds to and activates the receptor, triggering downstream signaling pathways. By activating Sig-1 receptor at the MAMs, cutamesine allows calcium translocation from the ER into the mitochondria rather than into the cytoplasm (Rodríguez et al., 2022). This mechanism is crucial for preventing cytosolic calcium overload, that can lead to ER stress and apoptosis (Linciano et al., 2023; Liu et al., 2022; Ngo et al., 2024). Sig-1 receptor activation promotes cell survival by reducing ER stress, a hallmark of many neurodegenerative diseases, thereby mitigating neuronal damage or death (Francardo et al., 2019; Hampel et al., 2020). Several studies have also reported anti-inflammatory effects of sigma receptor activation, including the downregulating of TNF-α expression, inhibition of NF-κB/p65 nuclear translocation, and suppression of MMP-9 expression (Sánchez-Blázquez et al., 2018; Wang and Zhao, 2019).

Despite the extensive evidence supporting the neuroprotective role of Sigma-1 receptor activation, most studies to date have focused on *in vivo* models of focal cerebral ischemia. Moreover, the direct effects of Sigma-1 receptor activation during global ischemic conditions remain insufficiently explored.

In the current study, we employed a pharmacological approach to elucidate the mechanisms by which cutamesine-mediated Sig-1 receptor activation modulates ischemic injury in rat organotypic, and acute hippocampal slices subjected to 30 min of oxygen and glucose deprivation (OGD), two *in vitro* models of global ischemia.

2. Material and methods

2.1. Materials

Cutamesine was purchased from Fisher Scientific (Cat. No. 13606, Hampton, NH, USA) and the antagonist, BD1047 (Cat. No. B8562-5MG) and the inserts (Cat. No. PICM03050) were purchased from Merck Life Science (San Giuliano Milanese, Milan, MI, Italy). The medium for tissue cultures was supplied by Merck Life Science (San Giuliano Milanese, MI, Italy).

2.2. Animals

Seven-day-old Wistar rat pups of both sexes (Charles River, MI, Italy) and six-week-old male Wistar rats (150–180 g body weight) (Envigo, Udine, Italy) were maintained in a controlled environment (23 ± 1 °C) with a 12-h light–dark cycle starting at 07:00, and had unrestricted access to water and a standard rodent diet.

The experimental procedures were conducted in accordance with the ethical policy of the University of Florence on the use of laboratory animals (17E9C.N.JBG/2023 and 17E9C.N.FCG/2021), with the Italian DL 26/2014 “protection of animals used for scientific purposes” and with the EU Directive 2010/63/EU. In line with national law and European directives, the study was carried out under the principles of the 3Rs, with maximal efforts to limit animal numbers and distress.

2.3. Rat organotypic hippocampal slice cultures

Organotypic hippocampal slice cultures were obtained from seven-day-old Wistar pups from both sexes (Charles River, MI, Italy) using procedures outlined in prior publications (Landucci et al., 2021). Organotypic slices were prepared at an early developmental stage in which sex-dependent differences are minimal (Campos et al., 2025; Nalvarte et al., 2021). In summary, McIlwain tissue chopper was used to obtain 420 μm transverse hippocampi slices. Then slices were selected with a microscope and four slices per insert were incubated onto semi-porous membrane inserts (Millipore, Milan, Italy, Cat. No. PICM03050; 30 mm diameter). Inserts were located in six-well tissue culture plates with 1.2 mL medium (50% Eagle’s minimal essential medium (Cat. No. M5650-500ML), 25% heat-inactivated horse serum (Cat. No. 26050-088), 25% Hanks’ balanced salt solution, (Cat. No. H6648-500ML), 5 mg/mL glucose (Cat. No. G8270-1KG), 2 mM L-glutamine (Cat. No. G7513-100ML), and 3.75 mg/mL amphotericin B (Cat. No. A2942-100ML) per well. Slices were maintained at 37 °C and 5% CO_2 for 2 weeks to allow tissue maturation with medium replacement every two days.

2.4. Oxygen and glucose deprivation in rat organotypic hippocampal slices

After the maturation period, slices were subjected to OGD for 30 min, by the incubation with glucose-free medium in the absence of heat-inactivated horse serum in an anoxic chamber at 37 °C saturated with 95% N_2/5% CO_2. After OGD, cultures were returned to normoxic incubator, and the medium was replaced with serum-free medium supplemented with 5 mg/mL glucose, thereby initiating the reoxygenation phase, and maintained under these conditions until neuronal injury was assessed 24 h later.

The drugs were present in the culture medium during 30 min of OGD and for the following 24 h recovery period. Cell damage was analyzed in organotypic slices using the fluorescent dye propidium iodide (PI, Cat. No. 81845-25MG) added to the medium 24 h after the ischemic insult. After 30 min-incubation fluorescence was observed by using an inverted fluorescence microscope (Olympus IX-50; Solent Scientific, Segensworth, UK) integrated with a xenon-arc lamp, a low-power objective (4 ×), and a rhodamine filter. Image-Pro Plus morphometric analysis software (Media Cybernetics, Silver Spring, MD, USA) was used for analyzing the digitized images obtained using a CCD camera (Diagnostic Instruments Inc., Sterling Heights, MI, USA) controlled by software (InCyt Im1TM; Intracellular Imaging Inc., Cincinnati, OH, USA).

Cell death was quantified in the CA1 hippocampal subfield by assessing the optical density of PI fluorescence using ImageJ (NIH, Bethesda, MD, USA).

Cutamesine and BD1047 were solubilized in deionized water at concentrations of 20 mg/mL and 11.4 mM, respectively. Stock drugs stored at –20 °C were diluted in culture medium immediately prior to application to cultures.

2.5. RNA extraction, retrotranscription and quantitative Real-Time polymerase chain reaction (RT-qPCR)

Total RNA from slices (4 slices/sample) was isolated using Trizol Reagent (Thermo Fisher Scientific, Milan, Italy, Cat. No. 15596026) (Landucci et al., 2023). After quqantification, one μg of RNA was retrotranscrbed using PrimeScript RT Reagent Kit (Diatech Lab Line Srl, Jesi, AN, Italy, Cat. No. RR047A).

Real-Time quantitative polymerase chain reaction (RT-qPCR) was carried out using Rotor-Gene 3000 Instrument (Qiagen, Milan, Italy) and was performed using SsoAdvanced TM Universal SYBR® Green Supermix (Bio-Rad, Milan, Italy, Cat. No 1725274) under the following conditions: 95 °C for 30 s, 95 °C for 5 s and 60 °C for 15 s for 45 cycles. Primers were purchased from Integrated DNA Technologies (Iowa,

USA). Ribosomal 18S RNA was used as the housekeeping. The sequences of the primers used read as follows: 78-kDa glucose-regulated protein (GRP78) forward 5′- GACCCTTACTCGGGCCAAAT −3′ and reverse 5′-TCCGCCAACCAGAACAATCT −3′; glucose-regulated protein 94 (GRP94) forward 5′- GGCAACTCTTCGGTCAGGAT −3′ and reverse 5′-TTTAAGCTGAGGCGGAGCAT −3′; activating transcription factor 6 (ATF6) forward 5′- CTTTCTCCGGCTTCCTCCAGTTGTTC −3′ and reverse 5′- TTGTTTCCAGGACCAGTGACAGGCTTC −3′; inositol requiring enzyme-1 (IRE1) forward 5′- GCA-GACTTTGTCATCAGCCTTCGCAG-3′ and reverse 5′- CGCCATTGGACA-CAAAGTGGGACATC-3′; protein kinase RNA-like endoplasmic reticulum kinase (PERK) forward 5′- GCACTGGATGCCGAGAATCATGGG −3′ and reverse 5′-TCGAGAAGGGACTCCACAGTGAAAGG −3′; Tumor Necrosis Factor-alpha (TNF-α) forward 5′- GCCAATGGCATGGATCTCAAAG −3′ and reverse 5′- AGGGCTCTTGATGGCAGAGAGG −3′; Interleukin-1 beta (IL-1β) forward 5′- AATGCCTCGTGCTGTCTGACCC −3′ and reverse 5′-TGGGTGTGCCGTCTTTCATCAC −3′; Matrix metalloproteinase-9 (MMP-9) forward 5′- CAGACGTGGGCAAATTCCAAACCTTCG −3′ and reverse 5′- TGGATGACAATGTCTGCTTCGAGCCC −3′; and 18S forward 5′-GGCGGCTTTGGTGACTCTAGATAACC −3′ and reverse 5′-CCTGCTGCCTTCCTTGGATGTGG −3′.

2.6. Western blot analysis

Western blot analyses were carried out as described in previous studies (Landucci et al., 2021). In brief, four slices from each sample were homogenized in 1% SDS, and total protein levels were measured using the bicinchoninic acid (BCA) protein assay. Protein samples (20 μg per lane) were loaded onto a 4–20% SDS-polyacrylamide gel (Bio-Rad, Milan, Italy; Cat. No. 4568093) for electrophoretic separation, followed by transfer onto nitrocellulose membranes using the Trans-Blot® Turbo system (Bio-Rad, Milan, Italy; Cat. No. 690BR041031). After, the membranes (Bio-Rad, Milan, Italy; Cat. Nos. 1704158 and 1704159) were blocked for 5 min using EveryBlot® Blocking Buffer (Bio-Rad, Milan, Italy; Cat. No. 12010020). Then, the membranes were incubated overnight at 4 °C with rabbit polyclonal antibodies against GRP78 (Invitrogen, Carlsbad, CA, USA, Cat. No. PA1-014A), GRP94, IL-1β (Abcam, Cambridge, London, UK Cat. No. AB13509 and Cat. No. AB254360), with the rabbit recombinant multiclonal MMP-9 (Abcam, Cambridge, London, UK, Cat. No. AB283575) all diluted 1:1000 in 20 mM tris-buffered saline-0.1% Tween20 (TBS-T) containing 5% non-fat dry milk, with monoclonal rabbit antibody against Phospho-NF-κB p65 (Ser536) (93H1) (Cell Signaling Technology, Beverly, MA, USA, Cat. No. 3333S), diluted 1:1000 in TBS-T containing 5% bovine serum albumin, and with monoclonal mouse antibodies against PERK, ATF-6α (Santa Cruz Biotechnology, Dallas, TX, USA, Cat. No. sc-377400; sc-166659;) diluted 1:500, and monoclonal mouse antibody against IRE1α (Santa Cruz Biotechnology, Dallas, TX, USA, Cat. No. sc-390960) diluted 1:1000, in 20 mM tris-buffered saline-0.1% Tween20 (TBS-T) containing 5% non-fat dry milk. As a loading control, monoclonal mouse antibody against β-actin (Merck Life Science, Milan, MI, Italy, Cat. No. A3854-200UL) was used. For immunodetection, membranes were incubated with horseradish peroxidase-conjugated anti-rabbit and anti-mouse secondary antibodies (1:3000 IgG from donkey; Merck Life Science, Milan, Italy; Cat. Nos. AP187P and AP181P) in TBS-T containing 5% non-fat dry milk. After washing, protein bands were revealed using chemiluminescence (ECL Plus; Bio-Rad, Milan, Italy; Cat. No. 1705061) and imaged with ChemiDoc (Bio-Rad, Milan, Italy). Densitometric quantification was performed using QuantityOne software (Bio-Rad, Milan, Italy). Results are shown as the mean ± SD and expressed as arbitrary units, which correspond to the normalized ratio of target protein levels to β-actin normalized to basal levels.

2.7. Acute rat hippocampal slices

Acute rat hippocampal slices were obtained as previously reported (Pugliese et al., 2006). In the present study, we selected male rats for the acute slice experiments accordingly with our previous studies (Pugliese et al., 2006; Venturini et al., 2023). Six weeks old male Wistar rats were anesthetized with isoflurane (Baxter, Rome, Italy) and sacrificed by decapitation. Hippocampi were isolated from the brain and transferred to ice-cold oxygenated (95% O_2 − 5% CO_2) artificial cerebrospinal fluid (aCSF) composed by (mM): NaCl 125, KCl 3, NaH_2PO_4 1.25, $MgSO_4$ 1, $CaCl_2$ 2, $NaHCO_3$ 25, and D-glucose 10. Transverse hippocampal slices (400 μm thick) were cut using a McIlwain Tissue Chopper (Mickle Laboratory Engineering Co. Ltd., Gomshall, UK) and allowed to recover for at least 1 h in oxygenated aCSF at room temperature before electrophysiological recordings were conducted. Recordings were carried out with the slice fully submerged in a chamber (0.8 mL) and continuously perfused with oxygenated aCSF (31–32 °C) at a constant flow of 2 mL/min. The tested compound was applied by superfusion and reached the slice in 60 s, a delay that was considered in the experimental analysis.

2.8. Extracellular recordings

Test pulses (80 μs, 0.066 Hz) were delivered using a bipolar nichrome electrode placed in the stratum radiatum of the CA1 hippocampal region to stimulate the Schaffer collateral-commissural pathway. Evoked field excitatory postsynaptic potentials (fEPSP) were recorded using borosilicate glass microelectrodes (2–10 MΩ, Harvard Apparatus Ltd., Edenbridge, UK), filled with 150 mM NaCl and positioned in the apical dendritic region of CA1 pyramidal cells. The recorded signals were amplified (200, BM 622, Mangoni, Pisa, Italy), digitized (sample rate, 33.33 kHz), and stored for subsequent analysis using the LTP software (version 2.30D; Anderson and Collingridge, 2001). After establishing stable evoked response, input–output curves were obtained by gradually increasing the stimulus intensity at the beginning of each experiment. The stimulation strength was then adjusted to evoke a synaptic response of about 40% of the maximal response and kept constant throughout the recording.

2.9. Oxygen and glucose deprivation in rat acute hippocampal slices

OGD was induced by perfusing hippocampal slices with glucose-free aCSF saturated with a gas mixture of 95% N_2 and 5% CO_2 (Venturini et al., 2023) for 30 min. Under these conditions, recovery of fEPSPs does not occurs, as this protocol consistently induces irreversible synaptic failure, as previously reported by our group (Pugliese et al., 2006). Cutamesine was applied 15 min prior OGD, during the deprivation, and for 5 min after. fEPSPs were continuously monitored in all conditions and never recovered their amplitude after a 30 min OGD. Anoxic depolarization (AD) was detected as a negative direct current (d.c.) potential shift during OGD, indicating membrane depolarization in cells located near the recording electrode (Farkas et al., 2008). The latency of AD was measured from the start of the OGD period and expressed in minutes, its amplitude was determined at the point of maximum negative deflection, reported in millivolts (mV) as positive values.

2.10. Statistical analysis

Data are expressed as mean ± SD. The statistical analysis in neuroprotection assays (PI fluorescence intensities) was carried out using one-way ANOVA followed by a post hoc Dunnett's and Tukey's w-test for multiple comparisons. Electrophysiological data were evaluated with unpaired Student's *t*-test. One-way ANOVA followed by post hoc Tukey test for multiple comparisons were used for analyzing gene expression and protein levels. GraphPad Prism v. 8 for Windows (GraphPad Software, San Diego, CA, USA) was used to perform all statistical analyses, considering a probability value (p) < 0.05 as significant.

3. Results

3.1. Cutamesine reduces CA1 injury in rat organotypic hippocampal slices exposed to OGD

To investigate the role of cutamesine in models of cerebral ischemia, we first employed rat organotypic hippocampal slices cultured for two weeks until maturation, an *in vitro* model routinely used in our laboratory for anatomical and molecular studies. By preserving both the structural and synaptic organization of the tissue, this model provides a reliable system to explore the consequences of chronic treatments (Mazzantini et al., 2025).

To assess the safety and tolerability of cutamesine under physiological conditions, rat organotypic cultures were exposed to rising concentrations of the compound (1–100 μg/mL) for 24 h, and neuronal integrity in the CA1 region was evaluated using PI fluorescence as shown in qualitative analysis (Fig. 1A–C). We selected the concentration range 1–100 μg/mL that corresponds to 2.7–270 μM in our experiments in organotypic hippocampal slice based on previously *in vitro* studies (Wang et al., 2020; Wang and Zhao, 2019). Our organotypic hippocampal slice model is cultured on semi-porous membrane inserts that impose a diffusion barrier for applied compounds. As a result, effective receptor engagement in organotypic slices typically requires drug concentrations approximately one order of magnitude higher than in monolayer cell cultures (Landucci et al., 2022). Qualitative and quantitative analysis demonstrated that cutamesine at 1 and 10 μg/mL did not induce detectable neuronal damage in the CA1 area compared to the control (Fig. 1B and D). In contrast, the highest concentration (100 μg/mL) significantly increased PI fluorescence compared to control ($p = 0.0102$), indicating cytotoxicity (Fig. 1C and D). These results suggest that cutamesine is non-toxic to hippocampal slices up to 10 μg/mL under physiological conditions. Based on these findings, the concentrations of 1 and 10 μg/mL were selected to evaluate its neuroprotective potential.

As shown in Fig. 1E, 30 min of OGD induced selective injury in the CA1 region of slices. This damage was significantly attenuated by incubation with 10 μg/mL cutamesine (Fig. 1F). Quantitative analysis (Fig. 1G) confirmed a dose-dependent neuroprotective effect, with maximal protection observed at 10 μg/mL ($p = 0.0008$ vs OGD); therefore, this concentration was selected for the subsequent set of experiments.

To determine whether Sig-1 receptor activation mediated the neuroprotective effect of cutamesine, the selective Sig-1 receptor antagonist BD1047 was applied at 100 nM a concentration previously shown to have no effect on OGD-induced injury *di per se* (Fig. 2D and E). Co-incubation with BD1047 abolished the neuroprotective effect of cutamesine (Fig. 2C), and this result was corroborated by quantitative analysis, which showed that BD1047 significantly reduced the neuroprotective effect of cutamesine ($p < 0.0001$ vs cutamesine) (Fig. 2E).

3.2. Cutamesine delays the onset of anoxic depolarization in acute hippocampal slices exposed to OGD

It is well established that ischemic conditions trigger a massive release of glutamate in neurons exposed to OGD, resulting in a strong

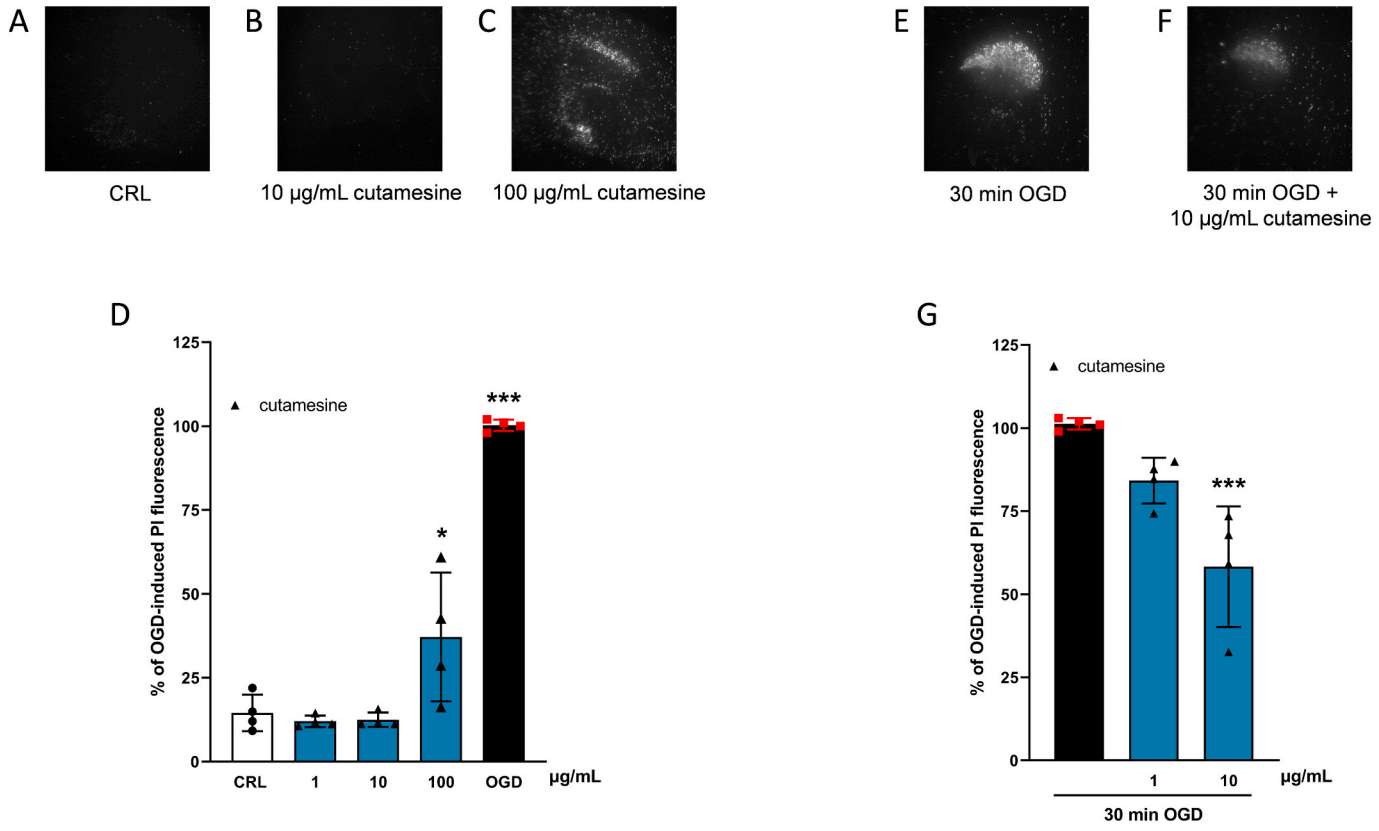

Fig. 1. Cutamesine reduces CA1 injury in organotypic slices exposed to 30 min of OGD. (A) Representative images of slice maintained under physiological conditions (baseline PI fluorescence). (B) Representative slice incubated with 10 μg/mL cutamesine in physiological condition displaying no damage in the CA1 area. (C) Representative slice incubated with 100 μg/mL cutamesine in physiological condition displaying diffuse PI signalling. (D) Quantification of PI fluorescence 24 h post-incubation with cutamesine (1–100 μg/mL) in physiological condition. (E) Representative slice showing intense PI fluorescence in the CA1 area after 30 min OGD. (F) Representative slice showing a decrease in CA1 damage after OGD in the presence of 10 μg/mL cutamesine. (G) Quantification of PI fluorescence after 24 h of incubation with cutamesine (1–10 μg/mL) in OGD conditions. Increasing doses of cutamesine progressively reduced the CA1 damage induced by OGD reaching significance at 10 μg/mL. Bars represent mean ± SD from at least four independent experiments performed in quadruplicate, from independent slice preparations. * $p < 0.05$ and *** $p < 0.001$ vs CRL (D) and vs OGD (G) (ANOVA + Dunnett's w-Test).

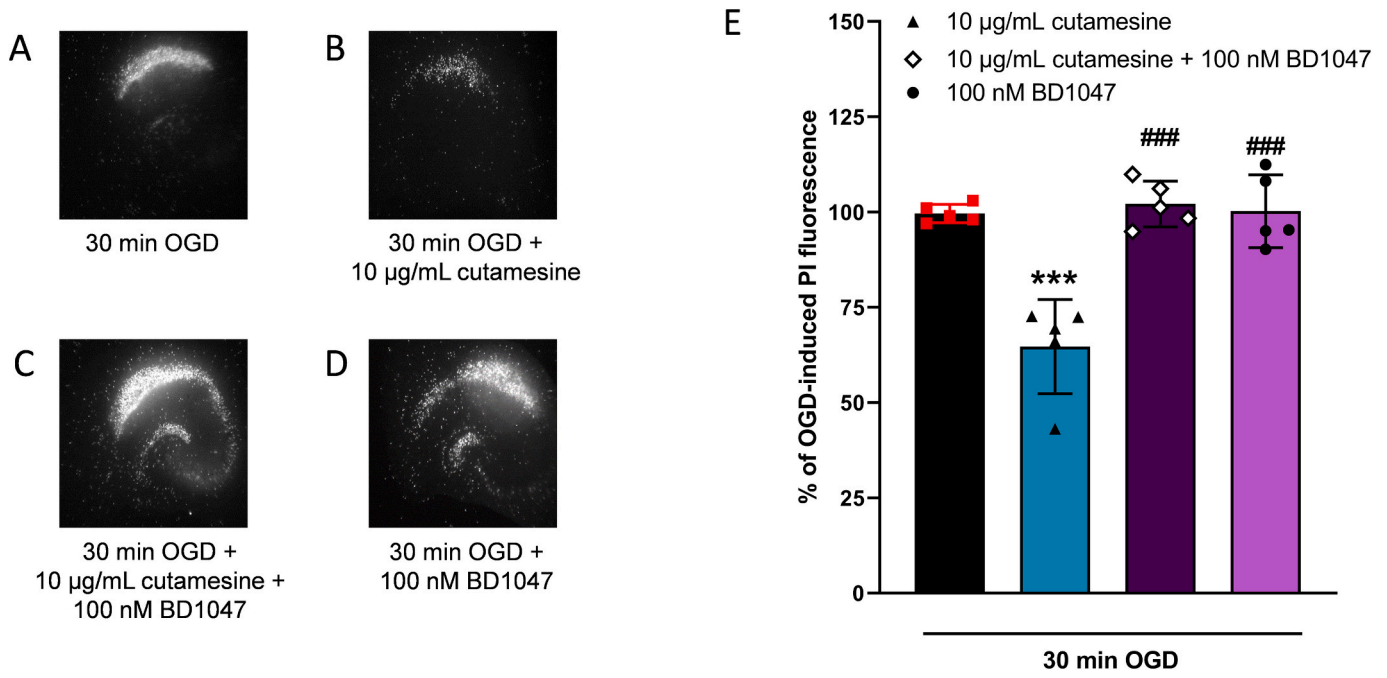

Fig. 2. BD1047 reduced the neuroprotective effect of cutamesine in the organotypic slices after 30 min of OGD. (A) Representative slice exposed to OGD (B) Illustrative slice exposed to OGD incubated with cutamesine (C) Representative slice exposed to OGD incubated with cutamesine plus BD1047 displaying CA1 damage similar to OGD. (D) Illustrative slice after 30 min of OGD in the presence of BD1047 displaying no different damage in comparison to OGD alone. (E) Quantitative analysis confirms that BD1047 reduced cutamesine's neuroprotective effect. Bars represent the mean ± SD from at least five independent experiments performed in quadruplicate. *** $p < 0.001$ vs OGD and ### $p < 0.001$ vs OGD plus cutamesine (ANOVA + Tukey's w-Test).

depolarization known as AD, which contributes to neuronal cell death (Heit et al., 2023). In this set of experiments, the effects of 1 µg/mL of cutamesine on neurotransmission in the CA1 region in acutely prepared hippocampal slices before and after 30 min of OGD insult were investigated. The concentration yielding maximal neuroprotection in our organotypic hippocampal slice model was 10 µg/mL. Given the diffusion constraints imposed by the semi porous membrane support in the organotypic system, we therefore selected a concentration one order of magnitude lower (1 µg/mL) for our acute slice experiments.

As shown in Fig. 3C, 30 min of OGD always induces AD onset in all slices. Under normoxic conditions, cutamesine had no significant effect on the amplitude of fEPSPs, from 1.07 ± 0.09 mV immediately before to 1.10 ± 0.11 mV after 15 min of drug application; similarly, no significant changes were observed in the fEPSP slope (Fig. 3A and B). However, during OGD, cutamesine significantly prolonged the latency to AD onset ($p = 0.001$ vs control) (Fig. 3D). In untreated slices after OGD insult, AD occurred with a mean latency of 6.61 ± 0.67 min and reached a mean peak amplitude of 6.52 ± 1.71 mV (Fig. 3E and F). Treatment with cutamesine prolonged the latency to AD onset to 8.84 ± 0.83 min. However, the amplitude of AD remained unchanged following drug treatment.

3.3. Cutamesine reduces the OGD-increased expression levels of the ER stress markers in organotypic hippocampal slices

ER stress is recognized as a central mediator of neuronal injury in cerebral ischemia, where prolonged disturbances in ER homeostasis can exacerbate neuronal loss in vulnerable regions such as the hippocampus (Han et al., 2021). To evaluate the effect of cutamesine on the activation of ER stress-related pathways induced by OGD in our model, we analyzed the gene and protein expression levels of GRP78 and GRP94 in the presence or absence of cutamesine or cutamesine plus BD1047.

As shown in Fig. 4, 30 min of OGD induced a significant increase in mRNA expression levels of GRP78 ($p = 0.0086$ vs control) and GRP94 ($p = 0.0201$ vs control) (Fig. 4A and B). When 10 µg/mL cutamesine was present in the incubation medium during OGD and the following 24 h reperfusion phase, it partially prevented the OGD-induced upregulation of these ER stress markers (Fig. 4A and B). Furthermore, Western blot analysis revealed a marked increase in GRP78 and GRP94 proteins levels following OGD when compared with control group (Fig. 4C-F). Treatment with 10 µg/mL cutamesine significantly reduced GRP78 ($p = 0.0457$ vs OGD) and GRP94 ($p = 0.0046$ vs OGD) protein levels increase induced by OGD (Fig. 4C-F). Consistent with the neuroprotective result described previously, the addition of BD1047 reduced the effects of cutamesine, but significantly so for GRP94 ($p = 0.0035$ vs cutamesine) (Fig. 4E and F).

To further assess the involvement of ER stress–related signaling, we analyzed the gene and protein expression of key components of the unfolded protein response (UPR), including ATF-6α, IRE1α, and PERK, in organotypic hippocampal slices subjected to OGD in the presence or absence of the drugs.

As shown in Fig. 5, 30 min of OGD induced a trend to increase in mRNA expression levels of ATF6 (Fig. 5A) but not of the IRE1 (Fig. 5B) and PERK (Fig. 5C). Cutamesine partially prevented the OGD-induced upregulation of ATF6 gene (Fig. 5A). Furthermore, Western blot analysis showed that OGD induced a significant increase in ATF-6α proteins levels ($p = 0.039$) and a trend of increase in IRE1α and PERK compared to control (Fig. 5D-I). In our experiments we analyzed the ATF6 band at 55-kDa which is the active form (Ron and Walter, 2007). Cutamesine was partially able to reduce the increased levels of these proteins induced by OGD (Fig. D-I).

3.4. Cutamesine reduces the OGD-increased expression levels of inflammatory markers in organotypic hippocampal slices

As previously reported, ischemia triggers a robust inflammatory response (DeLong et al., 2022). Inflammatory mediators such as TNF-α can trigger ER stress, thereby activating the UPR, establishing a regulatory loop that sustains inflammation and ultimately exacerbates ischemic injury (Aksu et al., 2025). OGD has been shown to elicit

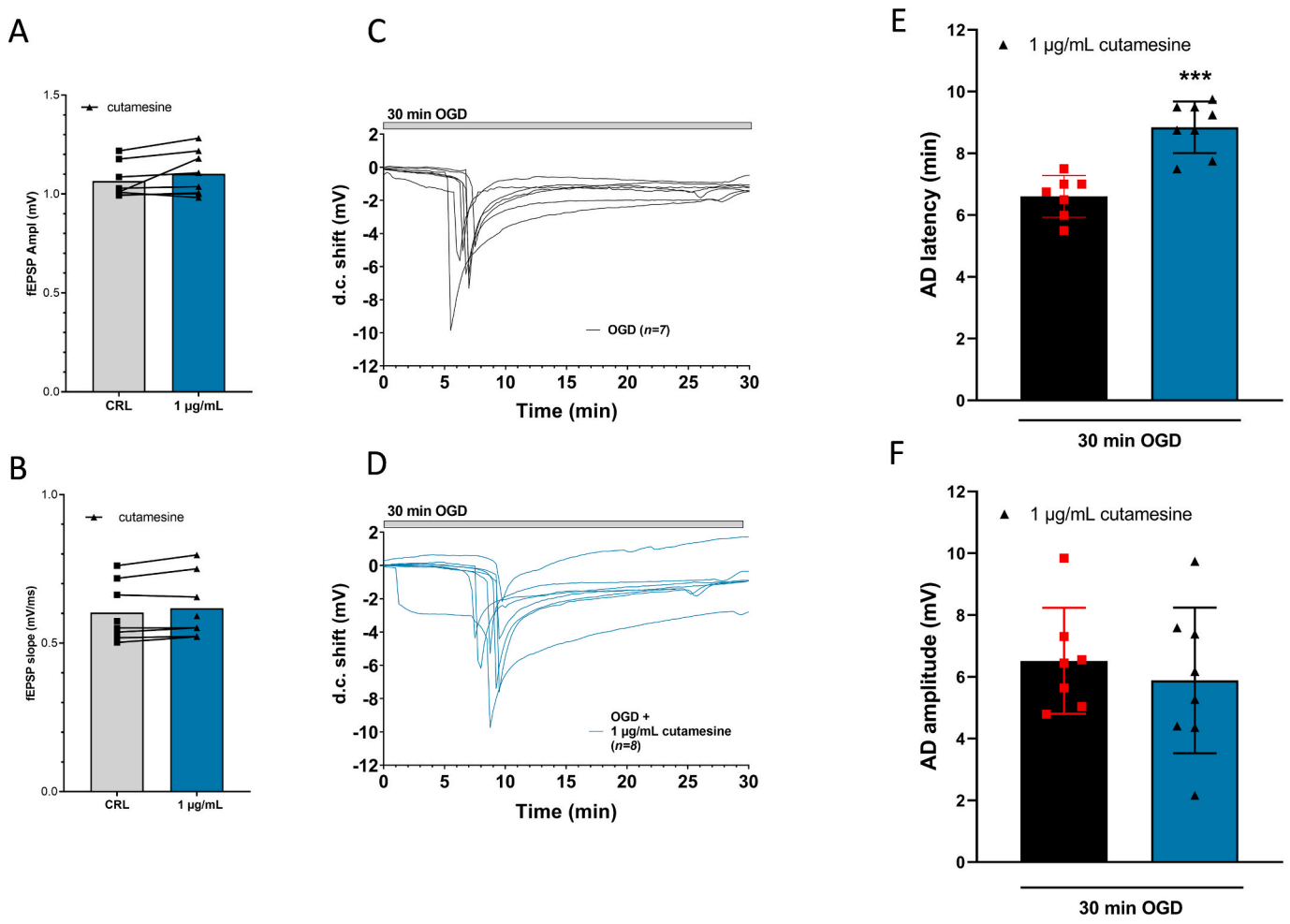

Fig. 3. Cutamesine delays the onset of anoxic depolarization (AD) after 30 min OGD in the CA1 region of acute slices. (A-B) Each value represents the fEPSP amplitude (A) or slope (B), before (CRL) or after cutamesine application. No significant differences were found. (C-D) Voltage traces of direct current (d.c) shift measured during 30 min of OGD are presented in each graph in the absence of drug (n = 7, from 6 rats, C) or in the presence of 1 µg/mL cutamesine (n = 8, from 5 rats, D). (E) AD latency recorded and AD amplitude (F) in CA1 in different conditions during OGD were represented in each column as the mean ± SD. Measurement of AD was performed at the onset of OGD. *** $p < 0.001$ vs. OGD (Unpaired Student's T-test).

inflammatory responses comparable to those induced by cerebral ischemia (Bryniarska-Kubiak et al., 2023).

To better understand the mechanisms underlying the neuroprotective and potential anti-inflammatory effects of cutamesine, we analyzed the expression levels of key inflammatory markers, including the cytokines TNF-α and IL-1β, as well as the enzyme MMP-9, using real-time qPCR and Western blot analysis.

As shown in Fig. 6, 30 min of OGD induced a significant increase in the mRNA expression levels of TNF-α ($p = 0.02$) (Fig. 6A), IL-1β ($p = 0.0421$) (Fig. 6B), and MMP-9 ($p = 0.0496$) (Fig. 6C) compared to control. Cutamesine treatment partially attenuated the OGD-induced upregulation of these proinflammatory genes (Fig. 6A-C).

The effect of OGD on inflammatory markers was also assessed by Western blotting. Qualitative and quantitative analysis revealed that 30 min of OGD significantly increased the expression levels of p-p65 ($p = 0.0146$ vs control) (Fig. 6D and E) and MMP-9 ($p = 0.026$ vs control) (Fig. 6H and I), and to a lesser extent IL-1β (Fig. 6F and G), compared to control. Cutamesine significantly reduced the OGD-induced increase expression of p-p65 ($p = 0.0305$ vs OGD) (Fig. 6D and E) and MMP-9 ($p = 0.0023$ vs OGD) (Fig. 6H and I), and partially decreased IL-1β levels (Fig. 6F and G). Moreover, 100 nM BD1047 significantly decreased the effect of cutamesine on MMP-9 expression ($p = 0.0004$ vs cutamesine) (Fig. 6D-I).

4. Discussion

Worldwide, cerebral ischemia is the second most common cause of mortality and a primary contributor to long-term disability (Wang et al., 2024). The progression of brain injury following an ischemic insult is commonly referred to as the ischemic cascade, which is characterized by a series of interconnected events, including energy failure, excitotoxicity, calcium overload, ER stress, inflammation, and ultimately, cell death (Ludhiadch et al., 2021; Ren et al., 2021). In recent years, numerous studies have identified the Sig-1 receptor as a novel molecular chaperone localized at the mitochondria-associated ER membrane (MAM). This receptor plays a critical role in brain plasticity, learning and memory process, and exerts neuroprotective effects under various stress conditions (Dai et al., 2022; Shi et al., 2021; Wang et al., 2023). Consequently, Sig-1 receptor signaling has emerged as a promising therapeutic target for neurodegenerative disorders, and particularly for the treatment of cerebral ischemia (Ngo et al., 2024).

In the current study, we employed a pharmacological approach to investigate the mechanisms by which cutamesine-mediated activation of Sig-1 receptor modulates ischemic injury for the first time in two *in vitro* models of global ischemia: rat organotypic and acute slices, subjected to 30 min of OGD. The neuroprotective activity of sigma-1 agonists, such as reducing cell death, preserving tissue integrity, and enhancing synaptic protein expression is well documented in several *in vivo* models of

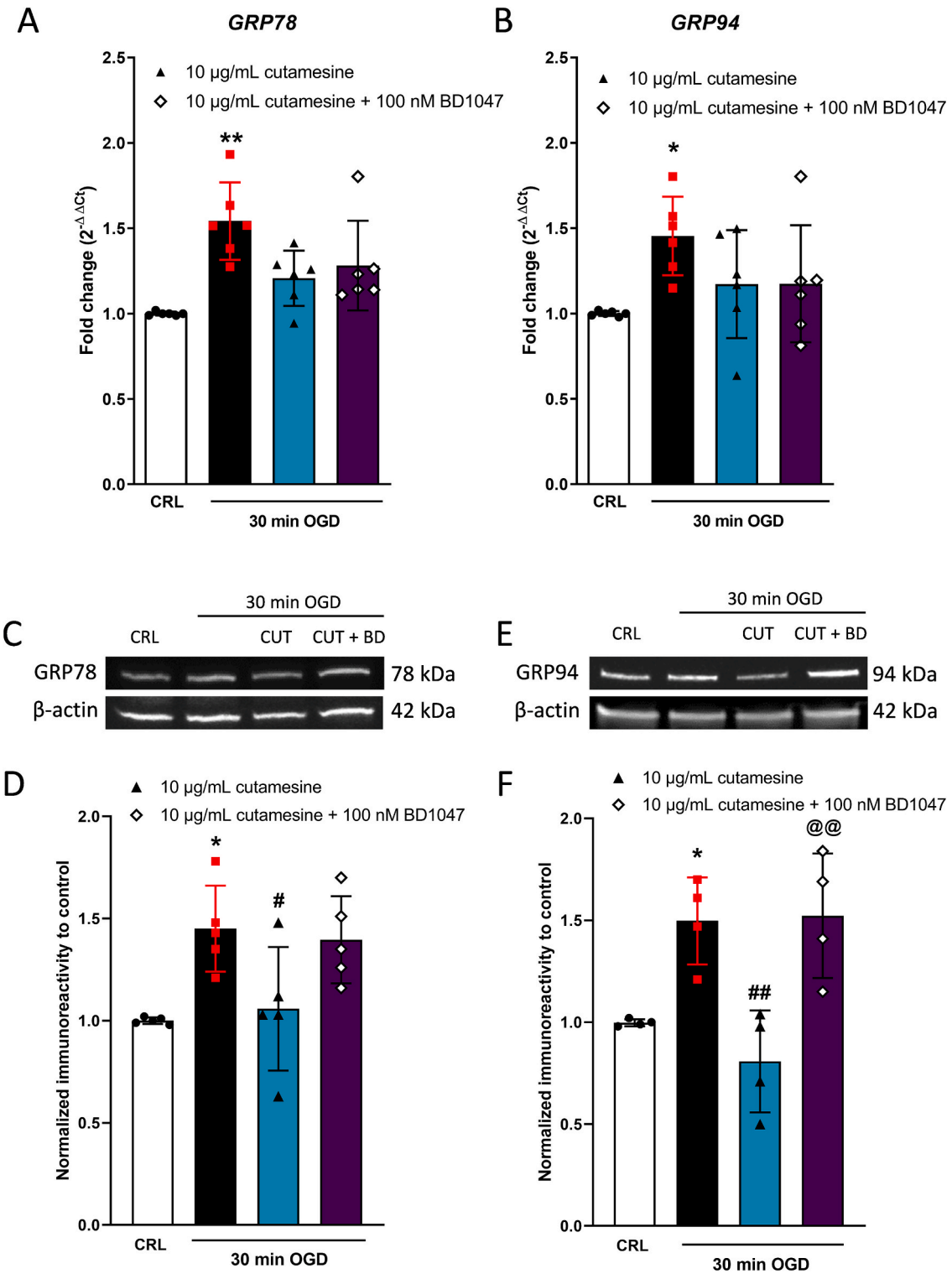

Fig. 4. Cutamesine reduces the OGD-increased expression levels of the ER stress markers in the organotypic slice. mRNA expression levels of (A) GRP78 and (B) GRP94 increased significantly after the ischemic insult, and this effect was prevented in part by 10 µg/mL cutamesine. (C, E) GRP78 or GRP94 or β-actin illustrative blots. (D, F) Immunoreactive bands quantification shows that 10 µg/mL cutamesine reduces the OGD-increased levels of ER-stress markers GRP78 (D) and GRP94 (F). BD1047 was able to reduce the cutamesine effect on ER stress markers. Bars represent the mean ± SD from at least six independent experiments for gene and at least four independent experiments for proteins. * $p < 0.05$ and ** $p < 0.01$ vs. CRL; # $p < 0.05$ and ## $p < 0.01$ vs. OGD; @@ $p < 0.01$ vs. OGD plus cutamesine (ANOVA + Tukey's w-test). CRL: control; CUT: 10 µg/mL cutamesine; CUT + BD: 10 µg/mL cutamesine + 100 nM BD1047.

stroke. These include transient middle cerebral artery occlusion (tMCAO) in mice (Vagnerova et al., 2006), both transient and permanent MCAO in rat, as well as primary cultures of rat astrocytes and neurons (Ruscher et al., 2011; Sato et al., 2014). Furthermore, activation of Sig-1 receptor has played a beneficial role in other models of neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), Parkinson's and Alzheimer's disease (Nguyen et al., 2017). The sigma agonists 1,3-di-o-tolyguanidine (DTG) and afobazole have been reported

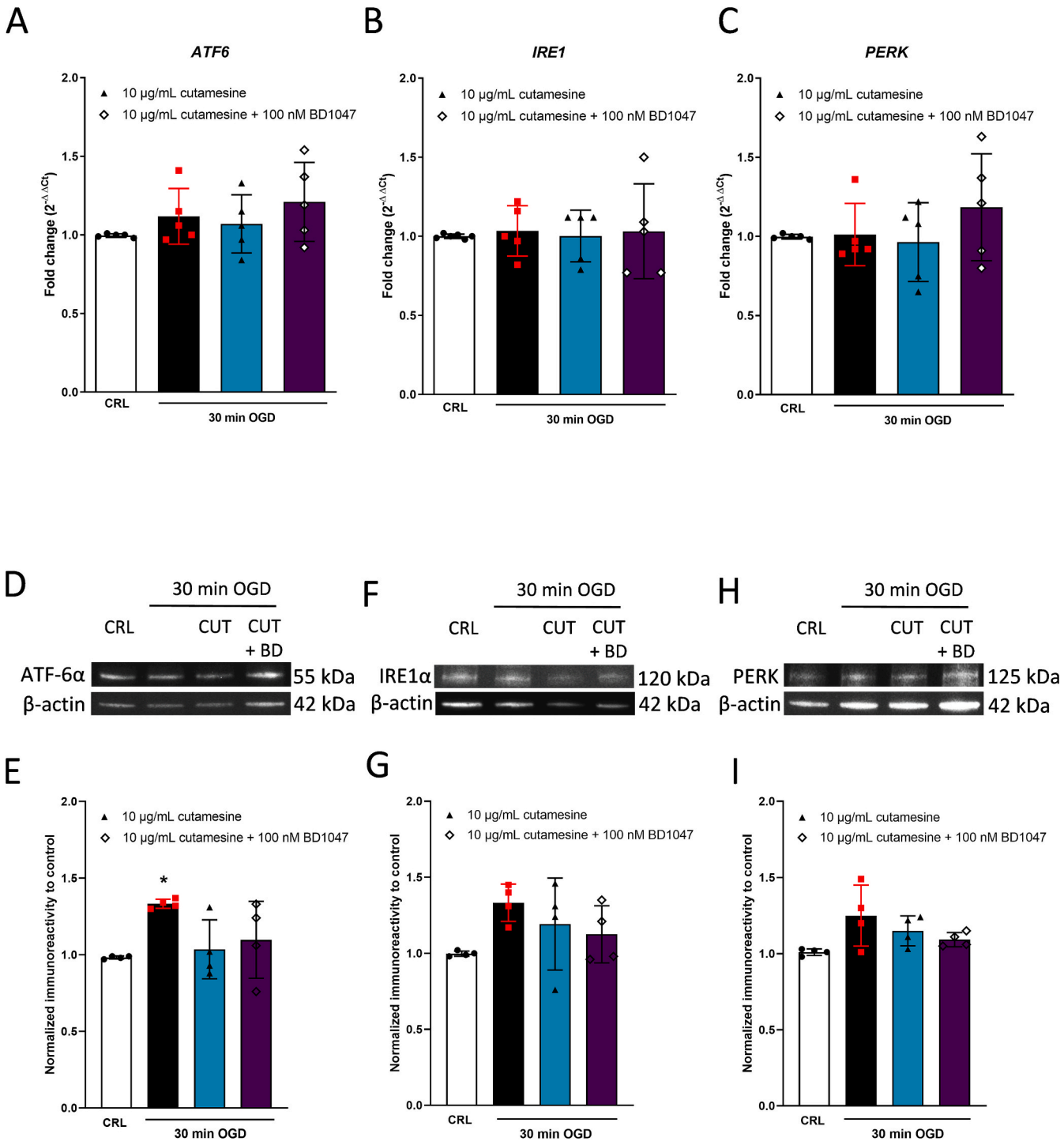

Fig. 5. Cutamesine attenuated the OGD-induced activation of ER stress–related pathways in organotypic hippocampal slices. OGD exposure was associated with a trend toward increased mRNA expression of (A) ATF6, which was partially reduced by treatment with 10 µg/mL cutamesine. In contrast, no significant changes were observed in the mRNA expression levels of (B) IRE1 or (C) PERK when compared with the control group. (D, F, H) Representative blots for (D) ATF-6α or (F) IRE1α or (H) PERK or β-actin. (E, G and I) Immunoreactive bands quantification shows that OGD increased (E) ATF-6α levels and cutamesine tends to reduce it. Bars represent the mean ± SD from at least four independent experiments. * $p < 0.05$ vs. CRL (ANOVA + Tukey's w-test). CRL: control; CUT: 10 µg/mL cutamesine; CUT + BD: 10 µg/mL cutamesine + 100 nM BD1047.

to increase neuronal survival and reduce infarct volume in a rat model of permanent MCAO (Ajmo Jr. et al., 2006; Katnik et al., 2014). Rodents underwent a permanent or transient MCAO and received Sig-1 receptor agonist cutamesine treatment demonstrated significantly improved sensorimotor recovery compared with vehicle-treated controls, although without a corresponding reduction in infarct size (Ruscher et al., 2011).

Cutamesine is a selective Sig-1 receptor agonist that has been studied in animal models of cerebral ischemia, where it has been shown to promote neuronal survival and enhance synaptic plasticity (Tanji et al., 2021; Wang and Zhao, 2019). Although a Phase II trial on cutamesine in acute ischemic stroke did not find overall clinical benefit, post hoc analysis showed significant improvement in patients with more severe deficits (Urfer et al., 2014), prompting continued preclinical

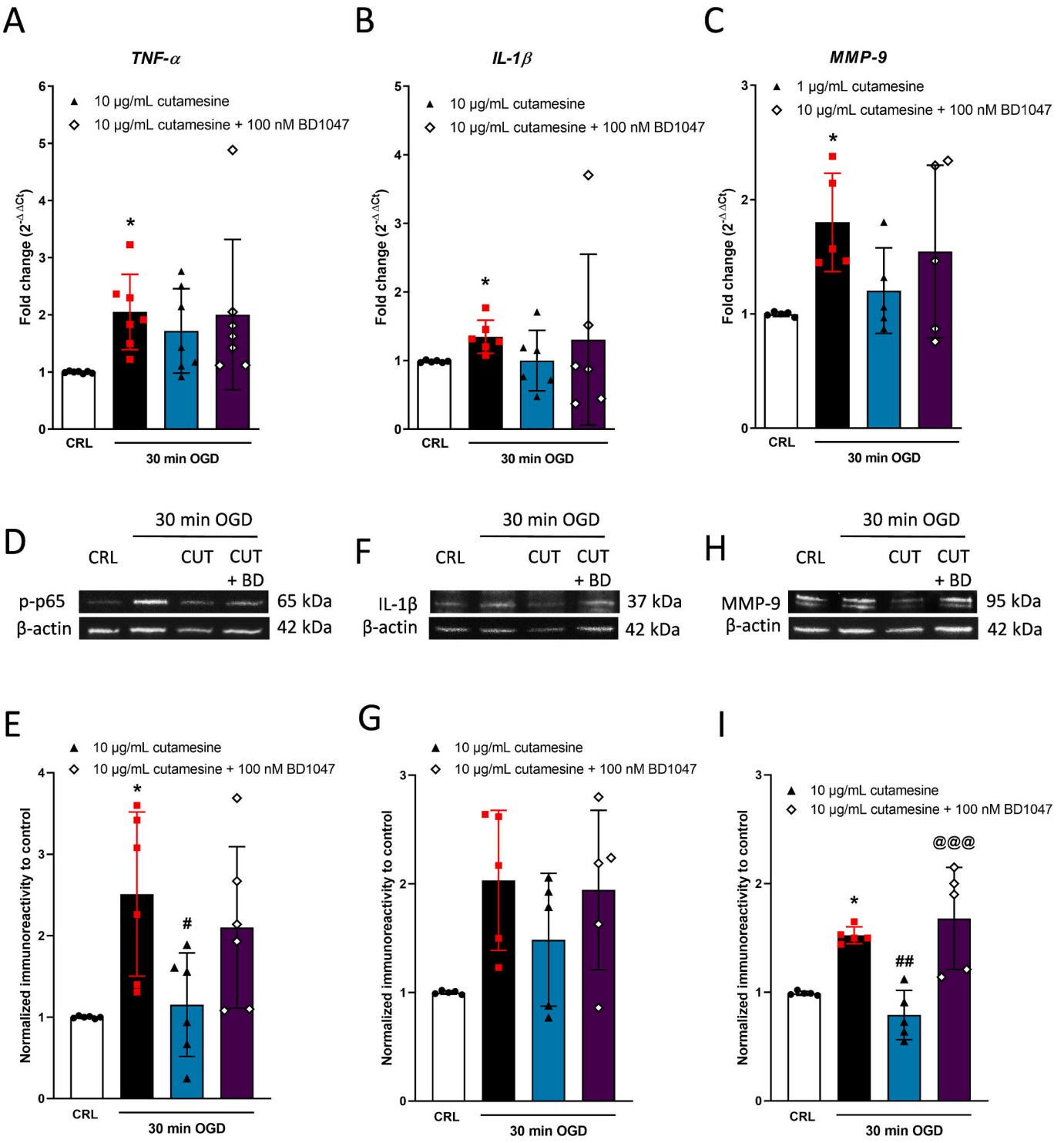

Fig. 6. Cutamesine reduces the OGD-increased expression of inflammatory markers in the organotypic slices. mRNA expression levels of (A) TNF-α, (B) IL-1β and (C) MMP-9 increased significatively after the ischemic insult, and this effect was reduced in part by 10 µg/mL cutamesine. (D, F, H) Representative blots for (D) p-p65 or (F) IL-1β or (H) MMP-9 or β-actin. (E, G and I) Immunoreactive bands quantification shows that cutamesine significantly reduces the OGD-increased levels of inflammatory proteins (E) p-p65 and (I) MMP-9. BD1047 reduced in part the anti-inflammatory effect of cutamesine reaching the significance only for (I) MMP-9. Bars represent the mean ± SD from at least five independent experiments. * $p < 0.05$ vs. CRL; # $p < 0.05$ and ## $p < 0.01$ vs. OGD; @@@ $p < 0.001$ vs. OGD plus cutamesine (ANOVA + Tukey's w-test). CRL: control; CUT: 10 µg/mL cutamesine; CUT + BD: 10 µg/mL cutamesine + 100 nM BD1047.

investigation of this selective Sig-1 receptor agonist in this study. In literature there are reports on brain concentrations after oral administration of cutamesine. Studies using [11C]SA4503 and positron emission tomography (PET) in humans have shown that SA4503 can effectively enter the brain and bind to sigma-1 receptors (Ishikawa et al., 2007). The ability of SA4503 to cross the BBB supports its development as a potential therapeutic agent for various neurological conditions (Weber et al., 2017; Ye et al., 2020).

Antagonists of the Sig-1 receptor have been widely used to confirm the putative neuroprotective effect of agonist compounds and to validate

their mechanisms of action. Among them, BD1047, unlike other antagonists such as BD1063 or S1RA, exhibits high affinity for Sig-1 receptor and does not exert neuroprotective effects on its own in ischemic models (Gaja-Capdevila et al., 2021; Sánchez-Blázquez et al., 2018). In accordance with other cerebral ischemia models, our findings provide for the first time evidence that cutamesine reduced CA1 neuronal injury caused by OGD in a dose-dependent manner in organotypic slices. At the highest tested dose (100 μg/mL) cutamesine induced cellular toxicity, as evidenced by increased PI fluorescence. Our data are in accordance with those of Miller et al. (2016) (Miller et al., 2016), who reported that low doses of cutamesine attenuated, whereas high doses enhanced the methamphetamine-induced hyperactivity. BD1047, the Sig-1 receptor antagonist, significantly reduced the neuroprotective effect of cutamesine, supporting the notion that its protective action is Sig-1 receptor-dependent.

This study also demonstrates that cutamesine significantly delays the onset of AD in acute rat hippocampal slices exposed to 30 min of OGD. Acute slices provide a complementary and valuable model for investigating the electrophysiological changes induced by ischemic insults, which are closely associated with excitotoxic damage. As previously reported (Venturini et al., 2023), 30 min of OGD consistently induces AD appearance in all slices. The ability of cutamesine to delay the onset of AD suggests that Sig-1 receptor activation may be involved in modulating ionic homeostasis during ischemic-like conditions.

The appearance of AD is a multifaceted process, primarily resulting from a massive efflux of K^+ into the extracellular space, along with the activation of Na^+ and Ca^{2+} channels, which together drive sustained depolarization of hippocampal neurons (Joshi and Andrew, 2001; Tanaka et al., 1997). This acute ionic imbalance compromises endoplasmic reticulum (ER) homeostasis, leading to protein misfolding and initiating the UPR (Wang et al., 2022). Moreover, elevated Ca^{2+} levels and/or excessive glutamate receptor activation represent additional mechanisms contributing to the induction of AD (Revah et al., 2016). Since Sig-1 receptor functions as a molecular chaperone and modulates several ionic channels, including calcium and ATP-sensitive potassium channels (Ren et al., 2021), its activation may contribute to preserve neuronal membrane potential by supporting mitochondrial function. In particular, it plays a central role in regulating ER-mitochondrial Ca^{2+} signaling by stabilizing inositol 1,4,5-trisphosphate receptors (IP_3Rs) and modulating ER Ca^{2+} release (Hayashi and Su, 2007). Upon activation by agonists such as cutamesine, Sig-1 receptor dissociates from ER chaperone BiP/GRP78, reinforces ER–mitochondria Ca^{2+} coupling, and facilitates the restoration of ER Ca^{2+} homeostasis (Weng et al., 2017). Notably, Sig-1 receptor ligand has been shown to inhibit the onset of AD in CA1 neurons, suggesting a broader neuroprotective role that extends beyond ER stress regulation to include membrane stabilization and modulation of neuronal excitability under ischemic conditions (White et al., 2012). Therefore, the neuroprotective effects of Sig-1 receptor likely involve both early modulation of membrane depolarization events and later attenuation of ER stress signaling.

Ischemic injury disrupts ER homeostasis, leading to the accumulation of misfolded proteins and UPR activation. While initially protective, prolonged ER stress contributes to neuronal dysfunction and apoptosis (Ren et al., 2021). Previous studies have demonstrated that activation of the Sig-1 receptor reduces ER stress-related markers in *in vivo* models of stroke (Morihara et al., 2018) and traumatic brain injury (Shi et al., 2022), as well as in an *in vitro* model of cardiac toxicity (Li et al., 2025), suggesting a broader modulatory role of Sig-1 receptor on the UPR. Under physiological conditions GRP78, a gatekeeper of mammalian UPR, binds to the transmembrane ER stress sensors; however, upon stress, GRP78 dissociates from these sensors, allowing UPR activation (Bhattarai et al., 2021). GRP94, an ER chaperone, also contributes to protein folding, particularly for proteins involved in immune responses and cell adhesion (Zhu and Lee, 2015).

The current study provides evidence that treatment with cutamesine significantly reduced the OGD-induced increase in the ER stress markers GRP78, GRP94, and ATF-6α in organotypic hippocampal slices, while no statistically significant modulation was observed in the other two branches of the UPR (IRE1 and PERK pathways) (Figs. 4 and 5). These findings support the hypothesis that sigma-1 receptor activation by cutamesine promotes cellular homeostasis, thereby reducing the need for sustained UPR engagement. This effect is reflected in the attenuation of ATF-6α signaling and the consequent limitation of GRP78 and GRP94 transcriptional induction. In this context, the selective modulation of distinct UPR branches observed in the present study is consistent with previous reports describing preferential upregulation of ATF-6, rather than robust activation of the IRE1 and PERK pathways, in primary neuronal cells exposed to hypoxic conditions (Gharibani et al., 2013; Liu et al., 2015; Prentice et al., 2017).

Cerebral ischemia triggers both UPR and pro-inflammatory cascades, with each process exacerbating the other and amplifying neuronal damage. Previous studies have reported a reduction in inflammatory responses following Sig-1 receptor activation in *in vivo* models of neuropathic pain (An et al., 2025), traumatic brain injury (Dong et al., 2016) and tMCAO model of cerebral ischemia (Zhang et al., 2023). NF-κB is a key transcription factor involved in the regulation of inflammatory genes, including cytokines, and is activated during cerebral ischemia (Ridder and Schwaninger, 2009). MMP-9 is an enzyme that is upregulated in response to ischemic insult, allowing neutrophil infiltration, and contributing to neuronal and glial cell death, thereby worsening the outcome (Lin et al., 2021; Turner and Sharp, 2016). In the present study, cutamesine significantly decreases the increase levels of p-p65 and MMP-9 induced by OGD (Fig. 6). These findings indicate that Sig-1 receptor activation by cutamesine modulates the pro-inflammatory NF-κB pathway by decreasing p-p65 protein levels, which may, in turn, attenuate ER stress pathway activation (Li et al., 2022), thereby interrupting the deleterious loop between ER stress and inflammation. MMP-9 also contributes to the amplification of the inflammatory response by promoting cytokine release and immune cell recruitment, effects that were mitigated by cutamesine treatment. Several studies have suggested that MMP-9 downregulation is mediated by suppression of NF-κB signaling (Li et al., 2022; Ong et al., 2017). Furthermore, the observed reduction in MMP-9 expression implies that cutamesine may help prevent pathological extracellular matrix degradation, a process that, *in vivo*, contributes to blood–brain barrier disruption and infiltration of inflammatory cells (Turner and Sharp, 2016).

The antagonist BD1047 has been widely employed to unravel the role of Sig-1 receptor in the beneficial effects of various putative drugs, (Ono et al., 2014; Wang and Zhao, 2019). The co-treatment with BD1047 reduced the effect of cutamesine on both GRP78 and GRP94 protein levels, but significantly only for GRP94. The partial blockade of cutamesine's effect by BD1047 in GRP78 may suggest that this effect is mediated only in part through Sig-1 receptor. This differential effect might be related to the distinct functional roles of these chaperones protein: GRP78 acts as a master regulator of ER stress and is involved in the early stages of the UPR, whereas GRP94 primarily supports the proper folding and maturation of a subset of complex proteins, particularly those related to inflammation and cell signaling, such as integrins and MHC-I molecules (Yang and Li, 2007).

Similarly, the co-treatment with BD1047 reduced the effect of cutamesine for MMP9 and partially for p-p65, may be due to the distinct functional and regulatory roles these molecules play in the inflammatory response. In this regard, p-p65 acts as a central transcription factor that initiates the inflammatory response by inducing the expression of various pro-inflammatory genes (Li et al., 2022). In contrast, MMP-9 contributes to neuroinflammation by remodeling the extracellular matrix and modulating cell–matrix interactions, which may influence neuronal damage, glial activation and synaptogenesis (Salamian et al., 2021; Virtuoso et al., 2024). Taken together, these findings indicate that cutamesine attenuates ischemia-induced ER stress, likely by disrupting the deleterious loop between ER stress, UPR and inflammation, an effect

that appears to be mediated, at least in part, by sigma-1 receptor activation. Furthermore, cutamesine alleviates inflammation by facilitating the proper folding of proteins related to immunity and cell adhesion, a mechanism closely linked to sigma-1 receptor activation.

Although organotypic cultures were prepared from animals of both sexes, no analyses or interpretations stratified by sex were performed. Sex-dependent differences in sigma-1 receptor signaling and ischemic vulnerability have been well documented in the adult brain and are largely influenced by estrogen-dependent mechanisms (Munguia-Galaviz et al., 2024) but not in developmental stage. Our slices were obtained in a developmental stage (7 days) at which circulating sex hormones are minimal and hormonal modulation of neural signaling is considerably less pronounced (Nalvarte et al., 2021; Sugiyama et al., 2009). Consequently, estrogen-mediated sex differences in sigma-1 receptor function are unlikely to substantially influence the observed ischemia-related responses under the experimental conditions used in this study. Nevertheless, we acknowledge that investigating potential sex-dependent differences would represent an important and relevant direction for future studies in experimental models using animals at more advanced developmental stages.

5. Conclusions

In conclusion, our results demonstrate that cutamesine provides significant neuroprotection in two complementary *in vitro* models of global cerebral ischemia. Although further *in vivo* studies are needed to overcome the limitations of our *in vitro* models, cutamesine appears to have therapeutic potential for the treatment of cerebral ischemia.

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CRediT authorship contribution statement

Alba Puente-Sanz: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Costanza Mazzantini:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Martina Venturini:** Methodology, Formal analysis, Data curation. **Francesca Mainolfi:** Methodology, Formal analysis, Data curation. **Amanda Herrero-González:** Methodology, Formal analysis, Data curation. **Anna Maria Pugliese:** Writing – review & editing, Supervision. **Arsenio Fernández-López:** Writing – review & editing, Supervision. **Domenico E. Pellegrini-Giampietro:** Writing – review & editing, Resources, Project administration, Funding acquisition. **Elisa Landucci:** Writing – review & editing, Writing – original draft, Supervision, Resources, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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