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# Sigma-1 Receptor Ligands Chlorpromazine and Trifluoperazine Attenuate $Ca^{2+}$ Responses in Rat Peritoneal Macrophages

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**Abstract**—Sigma-1 receptors are ubiquitous multifunctional ligand-regulated molecular chaperones in the endoplasmic reticulum membrane with a unique history, structure, and pharmacological profile. Sigma-1 receptors bind ligands of different chemical structure and pharmacological action and modulate a wide range of cellular processes in health and disease, including $Ca^{2+}$ signaling. To elucidate the involvement of sigma-1 receptors in the processes of $Ca^{2+}$ signaling in macrophages we studied the effect of sigma-1 receptor ligands, phenothiazine neuroleptics chlorpromazine and trifluoperazine, on $Ca^{2+}$ responses induced by inhibitors of endoplasmic $Ca^{2+}$–ATPases thapsigargin and cyclopiazonic acid, as well as by disulfide-containing immunomodulators Glutoxim and Molixan in rat peritoneal macrophages. Using Fura-2AM microfluorimetry we showed for the first time that chlorpromazine and trifluoperazine inhibit both phases of $Ca^{2+}$ responses induced by Glutoxim, Molixan, thapsigargin, and cyclopiazonic acid in rat peritoneal macrophages. The data obtained indicate the participation of sigma-1 receptors in a complex signaling cascade caused by Glutoxim or Molixan and leading to an increase in intracellular $Ca^{2+}$ concentration in macrophages. The results also indicate the involvement of sigma-1 receptors in the regulation of store-dependent $Ca^{2+}$entry in macrophages.

**Keywords:** trifluoperazine, chlorpromazine, sigma-1 receptors, peritoneal macrophages, intracellular $Ca^{2+}$ concentration

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$Ca^{2+}$ is a universal second messenger acting in cells of microorganisms, plants, and animals (Berridge et al., 1998; Carafoli, Krebs, 2016). Changes in the transport and intracellular $Ca^{2+}$concentration, $[Ca^{2+}]_i$, play a key role in triggering and regulating general and specialized cellular functions such as proliferation, growth, secretion, contraction, nerve impulse transmission, immune response, etc. (Berridge et al., 2000, 2003). In cells of the immune system (lymphocytes, mast cells, macrophages), $Ca^{2+}$ ions work at all stages of cell life, including development, activation, differentiation, production of cytokines, and, finally, cell death (Vig, Kinet, 2009; Trebak, Kinet, 2019).

Sigma-1 receptors, which have a unique history, structure, and pharmacology and modulate a wide range of cellular processes in health and disease, are important participants in the processes of $Ca^{2+}$ signaling in cells (Su et al., 2010, 2016; Rousseaux, Greene, 2016; Penke et al., 2018; Schmidt, Kruse, 2019; Aishwarya et al., 2021). The International Union of General and Clinical Pharmacology included sigma receptors in the list of receptors only in 2013 as ligand-regulated nonopioid intracellular receptors (Alexander et al., 2013).

Sigma-1 receptors are unique multifunctional ligand-regulated molecular chaperones localized in the endoplasmic reticulum membrane at the border with mitochondria (mitochondria-associated endoplasmic reticulum membrane (MAM)) (Su et al., 2010, 2016; Rousseaux, Greene, 2016; Schmidt, Kruse, 2019; Delprat et al., 2020; Aishwarya et al., 2021). In addition, they can translocate to the plasmalemma and interact with ion channels and other receptors, as well as also being found in the nuclear envelope, where they are involved in the regulation of transcription (Su et al., 2016). These receptors are expressed in various cell types, including cells of the immune system (Rousseaux, Greene, 2016; Penke et al., 2018; Aishwarya et al., 2021).

*Abbreviations:* $[Ca^{2+}]_i$, intracellular $Ca^{2+}$concentration; CPA, cyclopiazonic acid; TFP, trifluoperazine; CP, chlorpromazine.

The sigma-1 receptor was first cloned in 1996 from guinea-pig liver (Hanner et al., 1996) and human placental choriocarcinoma cells (Kekuda et al., 1996). It turned out that the sigma-1 receptor is a protein with a molecular weight of 25 kDa, containing 223 amino acids. The amino-acid sequence of the human sigma-1 receptor is unique and has no homologues among other mammalian proteins (Hanner et al., 1996; Ossa et al., 2017). In 2016, the three-dimensional structure of the human sigma-1 receptor was first established in Kruse's laboratory using crystallography methods (Shmidt et al., 2016; Kruse, 2017). This receptor was found to be a trimer consisting of three identical protomers. Each protomer contains one transmembrane domain (Shmidt et al., 2016, 2018; Alon et al., 2017; Ossa et al., 2017; Shmidt, Kruse, 2019).

Sigma-1 receptors have a very broad pharmacological profile. Their ligands are compounds of different chemical structure and pharmacological action: antidepressants (fluvoxamine, sertraline, imipramine), neuroleptics (haloperidol, chlorpromazine), analgesics (pentazocine), anxiolytics (afobazole), anticonvulsants (phenytoin), antitussives (dextromethorphan, carbetapentane) and antihistamines (chlorphenamine), narcotic drugs (methamphetamine and cocaine), and drugs used in the treatment of neurodegenerative diseases (amantadine, memantine, donepezil) (Cobos et al., 2008; Maurice, Su, 2009; Chu, Ruoho, 2016; Vavers et al., 2019; Voronin et al., 2020). Of the common structural features of the ligands, the cationic amino group and at least one aromatic ring should be noted. Typical neuroleptics (haloperidol, fluphenazine, chlorpromazine, trifluoperazine) have a high affinity for sigma-1 receptors (Tam, Cook, 1984).

Acting as chaperones, sigma-1 receptors interact with target proteins (ion channels, plasmalemma receptors, etc.) and modulate many cellular processes, including $Ca^{2+}$ signaling (Su et al., 2010, 2016; Schmidt, Kruse, 2019; Pontisso, Combettes, 2021). In the plasmalemma, they interact with voltage-dependent $Ca^{2+}$-, $Na^{+}$-, and $K^{+}$-channels, proton-activated ion channels (ASICs), NMDA receptors, G-protein coupled receptors (muscarinic acetylcholine receptors, μ-opioid and D1- and D2-dopamine receptors), and other target proteins (Su et al., 2010, 2016; Schmidt, Kruse, 2019). In the membrane of the endoplasmic reticulum, the sigma-1 receptor interacts with the type 3 inositol-1,4,5-triphosphate receptor, with another molecular chaperone, BiP protein (binding immunoglobulin protein) (Hayashi, Su, 2007), and STIM1 $Ca^{2+}$-sensor protein (Srivats et al., 2016). It was found that, when interacting with inositol-1,4,5-triphosphate receptors, sigma-1 receptors modulate $Ca^{2+}$ signaling in cells: $Ca^{2+}$ mobilization from the stores (Hayashi et al., 2000; Wu, Bowen, 2008) and $Ca^{2+}$ entry from the external medium (Monnet, 2005; Hayashi, Su, 2007; Pontisso, Combettes, 2021). They participate in the regulation of the store-dependent $Ca^{2+}$entry in cells (Brailoiu et al., 2016; Rosado, 2016; Srivats et al., 2016; Berlansky et al., 2021).

We have previously shown for the first time that the sigma-1 receptor antagonist neuroleptic haloperidol (a derivative of butyrophenone) significantly inhibits both phases of $Ca^{2+}$ responses caused by disulfide-containing immunomodulators Glutoxim® (disodium salt of oxidized glutathione with d-metal in nanoconcentration) and Molixan® (a complex of Glutoxim and inosine nucleoside) (Krutetskaya et al., 2017) and endoplasmic $Ca^{2+}$-ATPase inhibitors thapsigargin and cyclopiazonic acid (CPA) (Krutetskaya et al., 2018b) in rat peritoneal macrophages.

To confirm the involvement of sigma-1 receptors in the regulation of $Ca^{2+}$ signaling in macrophages, it seemed appropriate to investigate the effect of other, structurally different, sigma-1 receptor ligands on $Ca^{2+}$ responses induced by Glutoxim and Molixan, as well as thapsigargin (Thastrup et al., 1989) and CPA (Goeger et al., 1988), in rat peritoneal macrophages, which was the subject of this study.

The sigma-1 receptor ligands chlorpromazine (CP, aminazine, thorazine) (Itzhak et al., 1990; Hayashi, Su, 2004) and trifluoperazine (TFP, triftazine, stelazine) (Schuster et al., 1995; Hanner et al., 1996), belonging to the first generation typical neuroleptics (antipsychotic agents) of the phenothiazine series and having a long history of clinical application for the treatment of schizophrenia and other mental diseases (Dilsaver, 1993; Ayano, 2016), were used in our experiments.

## MATERIALS AND METHODS

### *Isolation and Cultivation of Rat Peritoneal Macrophages*

Experiments were carried out on cultured resident peritoneal macrophages of Wistar rats. The keeping of animals and all manipulations were performed in accordance with the regulations and requirements of the Order no. 267 of June 19, 2003, of the Ministry of Health of the Russian Federation "On Approval of the Rules of Laboratory Practice in the Russian Federation."

Resident macrophages were isolated from the peritoneal cavity of rats weighing 180–250 g according to the traditional method (Conrad, 1981; Randriamampita, Trautmann, 1987). Immediately after isolation, the cells were spherical and 10–20 μm in diameter. The cell suspension was placed in culture dishes with quartz glasses (10 × 10 mm) and cultured for 1–3 days at 37°C in medium 199 (pH 7.2) containing 20% bovine serum, glutamine (3%), penicillin (100 U/mL), and streptomycin (100 mg/mL). The α-naphthylesterase test confirmed that at least 96% of the cells in the monolayers were macrophages (Monahan et al., 1981).

The experiments were carried out at a temperature of 22–24°C 1–2 days after the start of cell cultivation. Quartz glasses with cells were placed in an experimental chamber filled with physiological solution of the following ionic composition (mM): 140 NaCl, 5 KCl, 1 $CaCl_2$, 1 $MgCl_2$, and 5 HEPES-NaOH, pH 7.3–7.4. The calcium-free medium differed in that it contained 1 mM EGTA and did not contain $CaCl_2$. The studied agents were added to macrophages in a calcium-free medium. To initiate $Ca^{2+}$ entry into the cells, 2 mM $Ca^{2+}$ were introduced into the external medium.

### *Measurement of $[Ca^{2+}]_i$*

A Fura-2AM fluorescent probe (Sigma-Aldrich, United States) was used. Macrophages were incubated for 45 min in physiological solution containing 2 μM Fura-2AM at 22–24°C. Glasses with stained cells were washed with physiological solution and transferred to the experimental chamber fixed on the table of Leica DM 4000B fluorescent microscope (Leica Microsystems, Germany). The fluorescence of the object was excited at wavelengths of 340 and 380 nm through the microscope objective. Narrow-band optical filters were used to isolate the corresponding parts of the spectrum. The emission was recorded at a wavelength of 510 nm using a specialized Leica DFC340FX video camera. The experiment was controlled using the ImageJ image processing system (Micro-Manager 1.4 plug-in).

The result of the measurements was the ratio of the fluorescence intensity of Fura-2AM when irradiated with light with a wavelength of 340 nm to the fluorescence intensity when irradiated with light with a wavelength of 380 nm ($F_{340}/F_{380}$), where $F_{340}$ is the fluorescence intensity of Fura-2AM associated with $Ca^{2+}$ and $F_{380}$ is the fluorescence intensity of Fura-2AM not associated with $Ca^{2+}$, reflecting changes in $[Ca^{2+}]_i$ in cells during measurements (Bruce, Elliott, 2000; Xie et al., 2002). To avoid photobleaching, measurements were taken every 20 s, irradiating the object for 2 s. A 10x objective with an 8 mm aperture was used in the experiments. $[Ca^{2+}]_i$ values were calculated using Grynkiewicz equation (Grynkiewicz et al., 1985). Statistical analysis was carried out using Student's *t*-test. Data are presented as mean and standard deviation. Each registration was obtained for a group of 40-50 cells. The figures show the results of typical experiments from six to eight independent ones. Differences were considered significant at $p \le 0.05$.

### *Reagents Used*

All reagents were purchased from Sigma-Aldrich (United States). Stock solutions of Fura-2AM (1 mM), CPA (10 mM), and thapsigargin (0.5 mM) were prepared in dimethyl sulfoxide. The drugs Glutoxim and Molixan were provided by PHARMA-VAM (St. Petersburg). Stock solutions of Glutoxim (50 mg/mL), Molixan (50 mg/mL), TFP (2 mg/mL), and CP (25 mg/mL) were prepared in water.

## RESULTS AND DISCUSSION

### *The Effect of Chlorpromazine and Trifluoperazine on $Ca^{2+}$ Responses Induced by Disulfide-Containing Immunomodulators*

Pharmacological analogues of oxidized glutathione (Glutoxim and Molixan) are used as immunomodulators and cytoprotectors in the complex therapy of bacterial, viral and oncological diseases (Borisov et al., 2001; Sokolova et al., 2002; Antushevich et al., 2013; Tolstoy et al., 2019). These drugs have a complex effect on the processes of redox regulation in cells, but the subtle biophysical mechanisms of their action are far from being fully understood.

In the present work, control experiments showed that incubation of macrophages for 20 min with 100 μg/mL Glutoxim (Fig. 1a) or 100 μg/mL Molixan (Fig. 2a) in a calcium-free medium causes a slowly growing increase in $[Ca^{2+}]_i$, reflecting $Ca^{2+}$ mobilization from intracellular $Ca^{2+}$ stores. On average, twenty minutes after the addition of agents, $[Ca^{2+}]_i$ increased from the basal level of 90 ± 18 to 135 ± 18 nM ($n = 7$; $p < 0.05$) for Glutoxim and 134 ± 20 nM ($n = 6$; $p < 0.05$) for Molixan. Upon introduction of 2 mM $Ca^{2+}$ into the external medium, a further increase in $[Ca^{2+}]_i$ was observed, reflecting the store-dependent $Ca^{2+}$ entry into the cytosol (Figs. 1, 2). On average, the increase in $[Ca^{2+}]_i$ during $Ca^{2+}$ entry was 223 ± 22 nM ($n = 7$; $p < 0.05$) and 202 ± 20 nM ($n = 6$; $p < 0.05$) for Glutoxim and Molixan, respectively.

In our experiments, it was found for the first time that preincubation of peritoneal macrophages with 25 μg/mL CP for 10 min before the administration of 100 μg/mL Glutoxim led to a significant suppression of both $Ca^{2+}$ mobilization from the stores (by 58.5 ± 4.6% , $n = 7$; $p < 0.05$) and the subsequent store-dependent $Ca^{2+}$ entry into cells (by 59.1 ± 6.1%, $n = 7$; $p < 0.05$) induced by Glutoxim (Fig. 1b). Preincubation of cells with 2 μg/mL TFP for 15 min prior to administration of 100 μg/mL Glutoxim also caused suppression of the $Ca^{2+}$ mobilization phase from the stores (by 36.2 ± 5.7%, $n = 8$; $p < 0.05$) and store-dependent $Ca^{2+}$ entry into macrophages (by 60.7 ± 7.1%, $n = 7$; $p < 0.05$), caused by Glutoxim (Fig. 1c).

Similar results were obtained in experiments on the effect of CP and TFP on $Ca^{2+}$ responses induced by 100 μg/mL Molixan in macrophages (Figs. 2b, 2c). Thus, suppression of the phase of $Ca^{2+}$ mobilization from the stores averaged 43.2 ± 8.9% ($n = 8$; $p < 0.05$) and 63.3 ± 2.4% ($n = 7$; $p < 0.05$), while the suppression of the store-dependent $Ca^{2+}$ entry into macrophages averaged 52.3 ± 9.1% ($n = 8$; $p < 0.05$) and

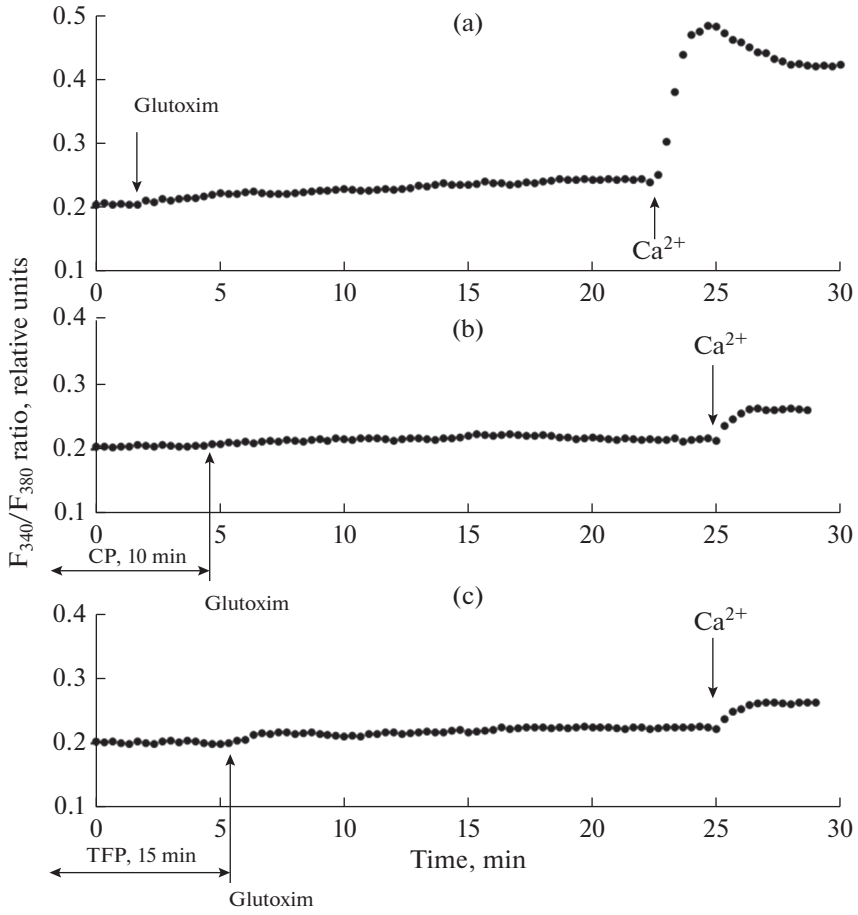


**Fig. 1.** The effect of chlorpromazine (CP, 25 μg/mL) and trifluoperazine (TFP, 2 μg/mL) on the $[Ca^{2+}]_i$ increase induced by Glutoxim in rat peritoneal macrophages. Here and in Figs. 2–4, the ratio of Fura-2AM fluorescence intensities at excitation wavelengths of 340 and 380 nm ($F_{340}/F_{380}$, arb. units) is along the *ordinate* axis; the *abscissa* axis is time. Stimulation conditions: (a) macrophages were incubated for 20 min in the presence of 100 μg/mL Glutoxim in a nominally calcium-free medium; then, $Ca^{2+}$ entry was initiated by introducing 2 mM $Ca^{2+}$ into the external medium; (b, c) macrophages were incubated for 10 min with CP (b) or for 15 min with TFP (c) in a calcium-free medium; then, 100 μg/mL Glutoxim was added; 20 min later, $Ca^{2+}$ entry was initiated by introducing 2 mM $Ca^{2+}$ into the external medium. Here and in Figs. 2–4, each recording was obtained for a group of 40–50 cells and represents a typical variant of six to eight independent experiments.

65.3 ± 5.0% ($n = 7$; $p < 0.05$) for CP and TFP, respectively.

### *The Effect of Phenothiazine Neuroleptics on $Ca^{2+}$ Responses Induced by Inhibitors of Endoplasmic $Ca^{2+}$ ATPase*

In control experiments, we found that the addition of 0.5 μM thapsigargin to macrophages in a calcium-free medium caused a slight increase in $[Ca^{2+}]_i$, reflecting $Ca^{2+}$ mobilization from the intracellular $Ca^{2+}$ stores (Fig. 3a). Subsequent addition of 2 mM $Ca^{2+}$ to the external medium resulted in the store-dependent $Ca^{2+}$ entry into the cytosol (Fig. 3a). On average, the increase in $[Ca^{2+}]_i$ during $Ca^{2+}$ entry was 160.2 ± 20.5 nM ($n = 7$; $p < 0.05$). We obtained similar results when using 10 μM CPA (Fig. 4a): on average, the increase in $[Ca^{2+}]_i$ during the phase of $Ca^{2+}$ mobilization from the stores, induced by CPA, was 37.8 ± 9.8 nM ($n = 7$; $p < 0.05$), while it was 150.2 ± 23.7 nM ($n = 7$; $p < 0.05$) during the store-dependent $Ca^{2+}$ entry into macrophages (Fig. 4a).

In our experiments, it was found for the first time that the preincubation of macrophages with 25 μg/mL CP in nominally calcium-free medium for 10 min before the administration of 0.5 μM thapsigargin causes a significant suppression of both phases of $Ca^{2+}$ responses induced by thapsigargin (Fig. 3b). Thus, suppression of the phase of $Ca^{2+}$ mobilization from the stores was 59.3 ± 8.2% ($n = 7$; $p < 0.05$), while the inhibition of store-dependent $Ca^{2+}$ entry was 68.2 ± 10.4% ($n = 7$; $p < 0.05$). Similar results were obtained in experiments using 10 μM CPA (Fig. 4b). The suppression of $Ca^{2+}$ mobilization from the stores amounted to 40.2 ± 9.1% ($n = 7$; $p < 0.05$), and the

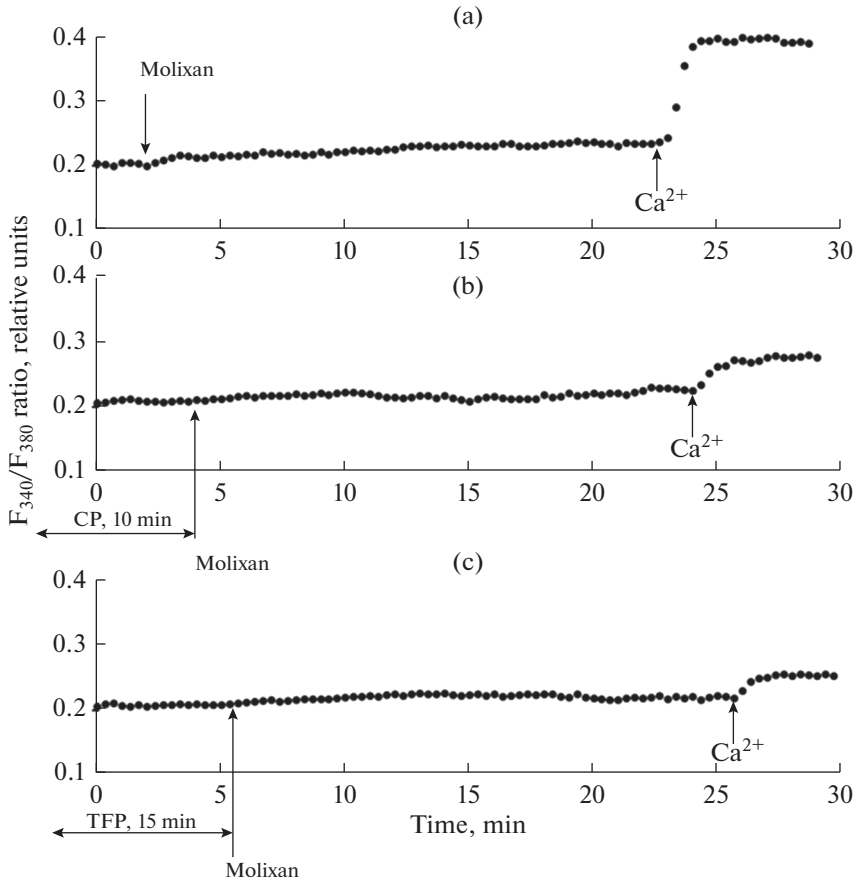


**Fig. 2.** The effect of CP and TFP on the $[Ca^{2+}]_i$ increase induced by Molixan (100 μg/mL) in rat peritoneal macrophages. (a–c) Conditions of preliminary stimulation in a calcium-free medium and subsequent initiation of $Ca^{2+}$ entry are the same as those indicated in the legend to Fig. 1.

suppression of the store-dependent $Ca^{2+}$ entry was 63.4 ± 11.5% ($n = 7$; $p < 0.05$).

Another phenothiazine neuroleptic, TFP, also significantly suppressed both phases of $Ca^{2+}$ responses induced by thapsigargin or CPA. It was shown that preliminary incubation of cells with 2 μg/mL TFP for 10 min before the introduction of 0.5 μM thapsigargin (Fig. 3c) caused suppression of the phase of $Ca^{2+}$-mobilization from the stores (by 59.0 ± 9.4%, $n = 7$; $p < 0.05$) and inhibition of the store-dependent $Ca^{2+}$ entry into macrophages (by 73.5 ± 11.2%, $n = 7$; $p < 0.05$), caused by thapsigargin (Fig. 3c). Similar data were obtained in experiments using 10 μM CPA (Fig. 4c). The suppression of $Ca^{2+}$ mobilization from the stores amounted to 40.1 ± 9.7% ($n = 7$; $p < 0.05$), and the suppression of the store-dependent $Ca^{2+}$ entry was 60.4 ± 10.8% ($n = 7$; $p < 0.05$). This confirms our earlier data that the preincubation of cells with TFP leads to suppression of the store-dependent $Ca^{2+}$ entry induced by inhibitors of endoplasmic $Ca^{2+}$–ATPase thapsigargin and CPA, in rat peritoneal macrophages (Krutetskaya et al., 2018a).

Thus, in the present work, we have shown for the first time on rat peritoneal macrophages that the sigma-1 receptor ligands, phenothiazine neuroleptics CP and TFP, suppress both phases of $Ca^{2+}$ responses caused by Glutoxim or Molixan, as well as thapsigargin and CPA, in peritoneal macrophages. The results are consistent with the data of studies by other authors, who found that sigma-1 receptor ligands, CP and TFP, suppress ~~the~~ $Ca^{2+}$ mobilization from the stores and subsequent store-dependent $Ca^{2+}$ entry, induced by ATP or thapsigargin in human leukemia cells (HL-60 line) (Harper et al., 1997; Harper, Daly 1999). It has also been shown that CP inhibits the store-dependent $Ca^{2+}$ entry induced by bradykinin or thapsigargin in rat pheochromocytoma cells (PC12 line) (Choi et al., 2001), as well as preincubation of cells with TFP leads to significant suppression of store-dependent $Ca^{2+}$ entry caused by thapsigargin~~,~~ in human embryonic kidney cells (HEK-293 line) (Wang et al., 2015). It was also found that sigma-1-receptor antagonists (compounds BD1063 and BD1047) inhibit ~~the~~ store-dependent $Ca^{2+}$ entry induced by histamine in human saphenous vein endothelial cells

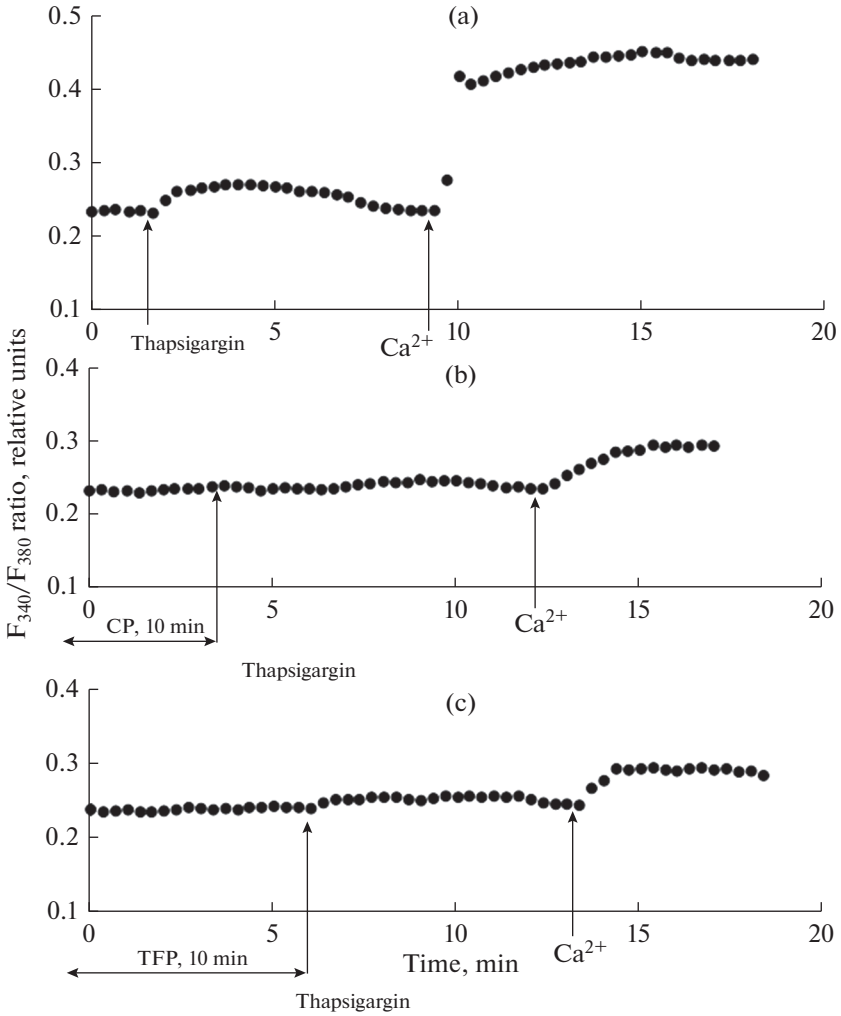


**Fig. 3.** The effect of CP (25 μg/mL) and TFP (2 μg/mL) on $Ca^{2+}$ responses induced by thapsigargin (0.5 μM) in rat peritoneal macrophages. (a–c) Experimental conditions are the same as those indicated in the legend to Fig. 1.

(Amer et al., 2013), while BD1063 significantly suppresses the store-dependent $Ca^{2+}$ entry caused by thapsigargin in human mammary adenocarcinoma cells (MCF7 line) (Gasparre et al., 2017). In addition, it is known that CP and TFP inhibit voltage-dependent $Ca^{2+}$ channels in various cell types. Thus, CP reversibly and dose-dependently blocks L- and T-type voltage-dependent $Ca^{2+}$ channels in mouse neuroblastoma cells (N1E-115 line) (Ogata, Narahashi, 1990; Ogata et al., 1990), R-type voltage-dependent $Ca^{2+}$ channels in human neurons (McNaughton et al., 2001), and L-type $Ca^{2+}$ channels in rat pheochromocytoma cells (PC12 line) (Ito et al., 1996), while TFP blocks L-type voltage-dependent $Ca^{2+}$ channels in rat smooth muscle cells (Nakazawa et al., 1993) and *Helix aspersa* neurons (Cruzblanca et al., 1998).

The results of this and our earlier works (Krutetskaya et al., 2017, 2018c) on the suppression by sigma-1 receptor ligands of $Ca^{2+}$ responses induced by Glutoxim and Molixan in macrophages indicate the involvement of sigma-1 receptors in the complex signaling cascade triggered by Glutoxim or Molixan and leading to an increase in $[Ca^{2+}]_i$ in rat peritoneal macrophages. The results also indicate that the combined use in clinical practice of the drugs Glutoxim or Molixan and phenothiazine neuroleptics CP and TFP is undesirable.

Our data also suggest the involvement of sigma-1 receptors in the regulation of the store-dependent $Ca^{2+}$ entry induced by disulfide-containing immunomodulators and inhibitors of endoplasmic $Ca^{2+}$–ATPase in rat peritoneal macrophages and allow us to consider sigma-1 receptors as a new regulatory component of the signaling complex of the store-dependent $Ca^{2+}$ entry in macrophages. Sigma-1 receptors may affect store-dependent $Ca^{2+}$ entry by modulating the binding between the main components of the protein complex of the store-dependent $Ca^{2+}$ entry -

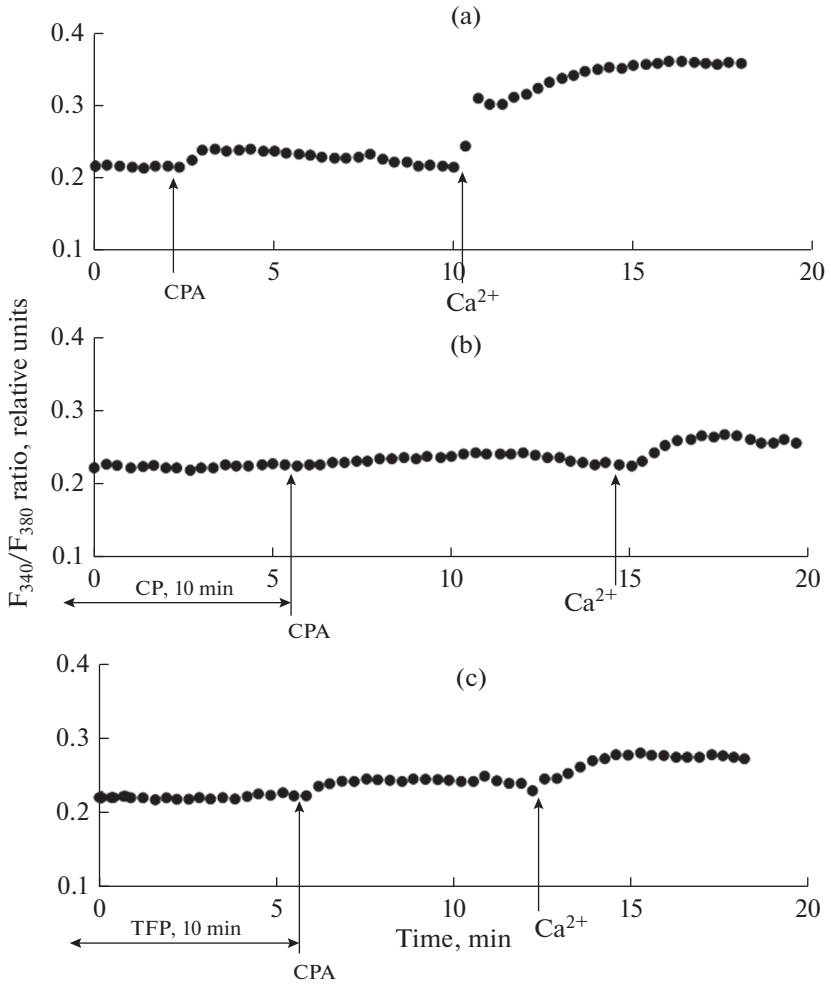


**Fig. 4.** The effect of CP (25 μg/mL) and TFP (2 μg/mL) on $Ca^{2+}$ responses induced by cyclopiazonic acid (CPA, 10 μM) in rat peritoneal macrophages. (a–c) Experimental conditions are the same as those indicated in the legend to Fig. 1.

STIM1 proteins in the endoplasmic reticulum membrane and Orai1 channels in the plasmalemma (Srivats et al., 2016).

The results may also contribute to a more detailed understanding of the molecular mechanisms of the pharmacological action of phenothiazine neuroleptics. In addition, the data obtained may be of importance for the treatment of diseases mediated by impaired functioning of sigma-1 receptors. Thus, changes in the subcellular localization, expression, and signaling functions of sigma-1 receptors are known to lead to the development of a wide range of human diseases (Su et al., 2010, 2016; Rousseaux, Greene, 2016; Schmidt, Kruse, 2019; Aishwarya et al., 2021). The involvement of these receptors in the pathophysiology of neuropsychiatric disorders (schizophrenia, anxiety disorders, depressive states, and dementia) (Hayashi, Su, 2004; Tsai et al., 2009, 2014; Ishikawa, Hashimoto, 2010; Hayashi, 2015; Voronin et al., 2020), neurodegenerative (Alzheimer's, Huntington's, and Parkinson's diseases; amyotrophic lateral sclerosis) (Ryskamp et al., 2017, 2019; Penke et al., 2018; Hayashi, 2019; Schmidt, Kruse, 2019; Yang et al., 2019; Herrando-Grabulosa et al., 2020; Zhemkov et al., 2021), oncological (Kim, Maher, 2017; Soriani, Rapetti-Mauss, 2017; Pontisso, Combettes, 2021) and cardiovascular (Stracina, Novakova, 2018; Aishwarya et al., 2021) diseases; pain syndromes (Merlos et al., 2017a, 2017b) and retinopathy (Wang et al., 2017; Smith et al., 2018) has been revealed. This made it possible to consider sigma-1 receptors as promising pharmacological targets for the treatment of these diseases.

Recently, the possible role of sigma-1 receptors in the pathophysiology of coronavirus infection (COVID-19) has also been studied. Evidence is emerging that sigma-1 receptors may be a promising therapeutic target in the treatment of patients with COVID-19. It is believed that sigma-1 receptors regulate the key mechanisms of the adaptive stress response of host cells and are involved in the early

stages of viral replication (Vela, 2020; Hashimoto, 2021).

Many repurposed drugs included in complex therapy regimens for patients with COVID-19 are often identified as sigma-1 receptor ligands. These include the neuroleptics haloperidol, CP, and TFP (Plaze et al., 2020; Vela, 2020). It is believed that CP is the most promising drug (Muric et al., 2020; Nobile et al., 2020; Plaze et al., 2020; Stip, 2020; Stip et al., 2020). There is evidence that cationic amphiphilic compounds, which include phenothiazine neuroleptics, have antiviral activity and inhibit the entry and replication of RNA viruses (Otręba et al., 2020; Vela, 2020; Gitahy Falcao Faria et al., 2021). Thus, CP has been shown to inhibit SARS-CoV-2 replication in monkey cells (VeroE6 line) and human alveolar epithelial cells (A549-ACE2 line) (Plaze et al., 2021). In addition, the sigma-1 receptor ligands haloperidol (Hoertel et al., 2021a) and CP (Hoertel et al., 2021b) have already passed clinical trials as drugs for the treatment of patients with COVID-19.

It is also known that viruses have evolved mechanisms to disturb host cell $Ca^{2+}$ homeostasis and increase $[Ca^{2+}]_i$, because $Ca^{2+}$ is essential for virus entry, replication, maturation and release (Zhoua et al., 2009; Chen et al., 2019). In this regard, the inhibiton of virus-induced $[Ca^{2+}]_i$ increase via inhibiting calcium release channels in the endoplasmic reticulum membrane (inositol-1,4,5-triphosphate receptors and ryanodine receptors) or $Ca^{2+}$ entry channels in the plasmalemma (voltage- and store-dependent $Ca^{2+}$ channels) is one of the approaches in the treatment of viral infections (Chen et al., 2019). Thus, it was found that blockers of the voltage-dependent $Ca^{2+}$ channels nifedipine and amlodipine reduce mortality and decrease the risk for mechanical ventilation in elderly patients with COVID-19 and hypertension (Solaimanzadeh, 2020; Zhang et al., 2020).

Thus, our data on the suppression of both phases of $Ca^{2+}$ responses, induced by disulfide-containing immunomodulators and inhibitors of endoplasmic $Ca^{2+}$–ATPases in rat peritoneal macrophages, by sigma-1 receptor ligands (CP and TFP), further confirm the versatility of the effects of phenothiazine derivatives and suggest that phenothiazine neuroleptics have therapeutic potential as sigma-1 receptor ligands.

## FUNDING

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## COMPLIANCE WITH ETHICAL STANDARDS

Experiments on animals were performed in accordance with generally accepted ethical international standards (International Guiding Principles for Biomedical Research Involving Animals, 1985) and the requirements of the Order no. 267 of June 19, 2003, of the Ministry of Health of the Russian Federation "On the Approval of the Rules of Laboratory Practice in the Russian Federation."

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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