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Article

BALB/c and C57BL/6 mouse strains influence gastric function outcomes with administration of cisplatin and dexamethasone

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Our aim was to evaluate the effects of cisplatin and dexamethasone alone and combined on gastric contractility and histomorphometry of BALB/c and C57BL/6 mice. BALB/c and C57BL/6 male mice (8-week-old) were randomly separated into: Control; Cisplatin (7.5 mg/Kg); Dexamethasone (2.0 mg/Kg); and Dexamethasone plus Cisplatin (2.0 mg/Kg of dexamethasone 1-hour prior to 7.5 mg/Kg of cisplatin). Drugs were administered intraperitoneally for three days. Body weight and food intake were evaluated on 2nd day. Alternating Current Biosusceptometry technique was employed to measure gastric contractions on 3rd day. Afterward, mice were killed for gastric histomorphometric analysis. Cisplatin decreased food intake and caused bradygastria in BALB/c mice; however, the amplitude of gastric contractions decreased in both BALB/c and C57BL/6. Dexamethasone and cisplatin combined restored the gastric frequency and food intake only in BALB/c, but drug combination reduced the gastric amplitude of contractions in both strains. Dexamethasone alone increased gastric mucosa thickness in C57BL/6 and decreased muscular thickness in BALB/c. In conclusion, the mouse strains presented differences in acute effects of cisplatin and dexamethasone alone and combined on gastric function. This reinforces the importance of choosing the appropriate mouse strain for studying the acute effects of drugs on the gastrointestinal tract.

Keywords: BALB/c. Bradygastria. C57BL/6. Gastric motility. Stomach.

INTRODUCTION

Mice are the species chosen for in vivo drug efficacy/toxicity studies (Clements *et al*., 2021). However, it has been observed that mouse strains respond differently to some drugs (Gosselin *et al*., 2017; Gong *et al*., 2019), highlighting the impact of the experimental model on data interpretation (Clements *et al*., 2021). Different mouse strains have distinctive physiological characteristics that impact immune response and also the gastrointestinal (GI) tract (Melgar, Karlsson, Michaëlsson, 2005; Sankoorikal *et al*., 2006; Miller *et al*., 2018; Soni *et al*., 2019; Gama *et al*., 2020).

Cisplatin (*cis*-diamminedichloroplatinum [II], Cis) is one of the most widely used chemotherapeutic agents due to its high efficacy and broad-spectrum; however, clinical use is limited by side effects (Qi *et al*., 2019). Cisplatin is associated with nausea, emesis, mucositis, malabsorption constipation, and diarrhea, which unless treated can lead to dose reductions or discontinuation of chemotherapy (Uranga *et al*., 2017; Liu *et al*., 2018; Shahid, Farooqui, Khan, 2018). In addition, cisplatin has been associated with anorexia, delayed gastric emptying,

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dysrhythmic gastric slow-wave, and morphologic changes in the GI tract (Viana-Cardoso *et al*., 2011; Uranga *et al*., 2017). Cisplatin is often used as a drug of choice to study emesis and the effect of anti-emetics in animal models (Shahid, Farooqui, Khan, 2018). Rodents do not have a vomiting reflex but may show nausea-like behaviors such as a reduction in food intake, an increase in non-nutritive substance intake (pica behavior), and a delay in gastric emptying (Perše, 2021). It has been demonstrated that cisplatin-induced pica behavior is affected by the mouse strains (Liu *et al*., 2005; Yamamoto, Okui, Yamatodani, 2018), although gastrointestinal motility disorders have not been directly assessed.

Antiemetic drug therapy is important to prevent chemotherapy-induced side effects (Yang, Wu, Liaw, 2016). Dopamine D_2 receptor antagonists, serotonin 5-HT_3 receptor antagonists, neurokinin NK_1 receptor antagonists, and corticosteroids are the drugs clinically used to prevent vomiting (Navari, Aapro, 2016). However, recovery of GI function may be an important factor in the treatment of nausea (Sanger, Broad, Andrews, 2013). Dexamethasone is a corticosteroid used in prophylaxis for chemotherapy-induced nausea and vomiting in combination with other drugs (Natale, 2015). Improvements in food intake have also been observed after treatment with dexamethasone (Yamamoto, Okui, Yamatodani, 2018). However, the mechanism by which it prevents chemotherapy-induced nausea and vomiting is still unclear (Obara *et al*., 2018), especially regarding gastrointestinal motor function.

The role of GI motility is the key to understanding the pathophysiology of symptoms related to the side effects of drugs and their prevention and management as well (Camilleri, Linden, 2016). Thus, our work aimed to evaluate the effects of cisplatin and dexamethasone alone or combined on the gastric contractility and morphometric of BALB/c and C57BL/6 mouse strains.

MATERIAL AND METHODS

Animals

Mouse strains were obtained from the Matrices Animal Facility at the University of São Paulo - USP. BALB/c (weighing 25-30 g; n = 28) and C57BL/6 (weighing 18-22 g; n = 28) male mice aged 7-8-week-old were used in this study. The mice were kept in an enriched environment, individually housed in home cages under controlled conditions of temperature (22±2° C), humidity (60±5%), and 12-hour light/dark cycle with free access to standard laboratory chow pellets (Purina®, Brazil) and filtered water before the experiments (Gama *et al*., 2020).

All experimental procedures were approved by the Ethics Committee on the Use of Animals of the Bioscience Institute of São Paulo State University - UNESP (protocol number 776) according to the Guidelines for Ethical Conduct in the Care and Use of Experimental Animals, and reported using the ARRIVE criteria.

Surgical procedures

After fasting for at least 6 hours, all the animals were anesthetized intraperitoneally (IP) with 85 mg/Kg ketamine (Cetamin®, Syntec, Brazil) and 8.5 mg/Kg xylazine (Xilazin®, Syntec, Brazil) and submitted to a laparotomy. A magnetic marker (diameter 4.0 mm; height 1.0 mm) was fixed with cyanoacrylate glue in the seromuscular layer of the stomach, 4.0 mm away from the limiting ridge.

Experimental protocol

Seven days after surgical recovery, twenty-eight animals of each strain were randomly separated, by a computer-generated sequence, into four groups: a) Control - BALB/c (n=7) and C57BL/6 (n=7) which received an injection of the saline solution in a volume equal to drugs (0.3 mL); b) Cis - BALB/c (n=7) and C57BL/6 (n=7) which received an injection of 7.5 mg/Kg Cisplatin (Fauldcispla® 10 mg, Libbs Farmacêutica Ltda, Brazil); c) Dex - BALB/c (n=7) and C57BL/6 (n=7) which received an injection of 2.0 mg/Kg dexamethasone (Decadron®, Aché Laboratories, Brazil); and d) Dex+Cis- BALB/c (n=7) and C57BL/6 (n=7) which received an injection of 2.0 mg/Kg dexamethasone 1 hour before treatment with cisplatin (Malik *et al*., 2007; Yamamoto, Yamatodani, 2018). All the drugs and saline solution were administered intraperitoneally.

The body weight was evaluated daily throughout the three days of the experiment. Food intake (24-hour consumption) was assessed during the second day of

treatment and normalized per gram body weight in all groups. Gastric contractility was evaluated in all groups BALB/c and C57BL/6 after the third dose of drugs or saline. Afterward, all the animals were killed by anesthetic overdose (300 mg/Kg ketamine plus 30 mg/Kg xylazine, IP). A laparotomy was performed to collect the stomach for morphological analysis. Figure 1 illustrates the timeline of the study protocol.

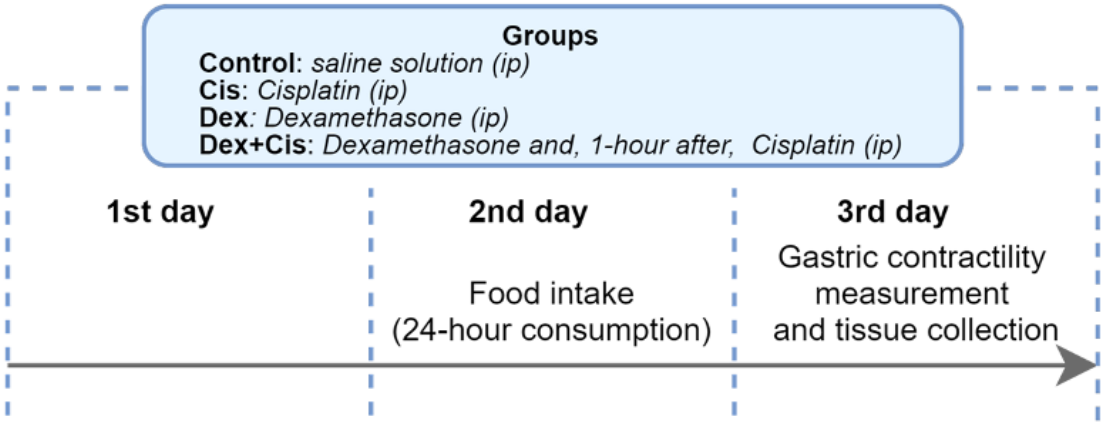

FIGURE 1 - Experimental setup for the study protocol. Drugs or saline were administered once daily for three days. Food intake was assessed after the first 24h post drugs administration; contractility analysis and stomach collection for histology were performed after 3rd dose administration.

Gastric contractility measurements

Gastric contractility was evaluated using the Alternating Current Biosusceptometry (ACB) technique (Br4-Science®, Brazil) (Américo *et al*., 2010).

Briefly, the ACB technique uses sensors that are an assembly of excitation and detection coils able to generate magnetic fields to detect the response from a magnetic marker. Contractility waves are detected as signals from the magnetic marker fixed in the seromuscular layer in response to a magnetic field applied by the sensor, according to the movement or distance of the animal's abdominal surface in relation to the sensor. Detailed technical information was reported earlier (Corá *et al*., 2005; Américo *et al*., 2010).

For gastric contractility measurements, mice fasted for 12 hours, during which the animals had water *ad libitum*. After ingesting 250 mg of standard laboratory chow, BALB/c and C57BL/6 groups were anesthetized intraperitoneally with 75 mg/Kg ketamine (Cetamin®, Syntec, Brazil) plus 2.5 mg/Kg acepromazine (Acepran®, Vetnil, Brazil). The animals were then laid supine and the ACB sensor was placed on the stomach surface towards recording the magnetic signals continuously for 20 minutes at a sampling rate of 20 Hz, by using a multichannel recorder (MP100 System; BIOPAC, Santa Barbara, CA, USA) (Américo *et al*., 2010).

Signals from the gastric contractility data were blindly analyzed in MatLab® (R2015a, Natick, MA, USA) by visual inspection and Fast Fourier Transform (FFT). The highest frequency peak for each FFT was determined as the dominant gastric frequency and the lowest was the intrinsic noise of the signal. Gastric frequencies were expressed as cycles per minute (cpm). The amplitude of contractions was determined by the ratio between the intensity of the gastric peak (P) and the noise peak intensity (P') and was expressed in decibels (dB) as follows: $A = 10 \log_{10} (P/P')$ (Lu *et al*., 2005; Gama *et al*., 2020). Normogastria was defined as a range of frequencies with 2SD (standard deviation) of the gastric frequency obtained in the control groups. The average values that were below this frequency range were classified as bradygastria, whereas average values above were classified as tachygastria (Marques *et al*., 2014).

Gastric morphometry

As described earlier, animals were killed for tissue collection. Stomachs were removed and immersion-fixed for 24 h in 10% buffered formalin. From then on, tissues were embedded in paraffin to be cut into 4 mm-thick sections and stained with hematoxylin and eosin (HE). HE staining was used for morphometric analysis of the thickness of the gastric muscular and mucosa. The images were captured using an Eclipse E200-Nikon optical microscope (Nikon, Japan), in objective x10, equipped with a 5.0 MP digital camera system (model ISH 500, Opton, Brazil), connected to a computer, and with an image capture program (TCapture). Ten measurements for each structure (mucosa/muscular) per animal were made (Pini *et al*., 2016). All morphometric measurements were blindly analyzed using ImageJ software (NIH, USA).

Statistical analysis

Data normally distributed (according to the Shapiro-Wilk test) were expressed as mean ± SD, and analyzed using one-way analysis of variance (ANOVA) followed by Dunnet's test, only if F achieved $p<0.05$, and there was no significant variance in homogeneity. Morphometric analysis was presented as median ± range, and the statistical variation among groups was tested by Kruskal-Wallis's test followed by Dunn's test. Values of $p<0.05$ were considered statistically significant.

RESULTS

BALB/c and C57BL/6 mice did not show significant changes in body weight during treatment with cisplatin, dexamethasone, or with both drugs simultaneously (Figure 2A). Cisplatin reduced the relative food intake in BALB/c animals, but not in C57BL/6 (Figure 2B). Dexamethasone did not affect the relative food intake and body weight in BALB/c mice; when combined with cisplatin, it prevented the reduction in food intake caused by cisplatin alone. In C57BL/6 mice, dexamethasone alone or combined with cisplatin did not change the relative food intake.

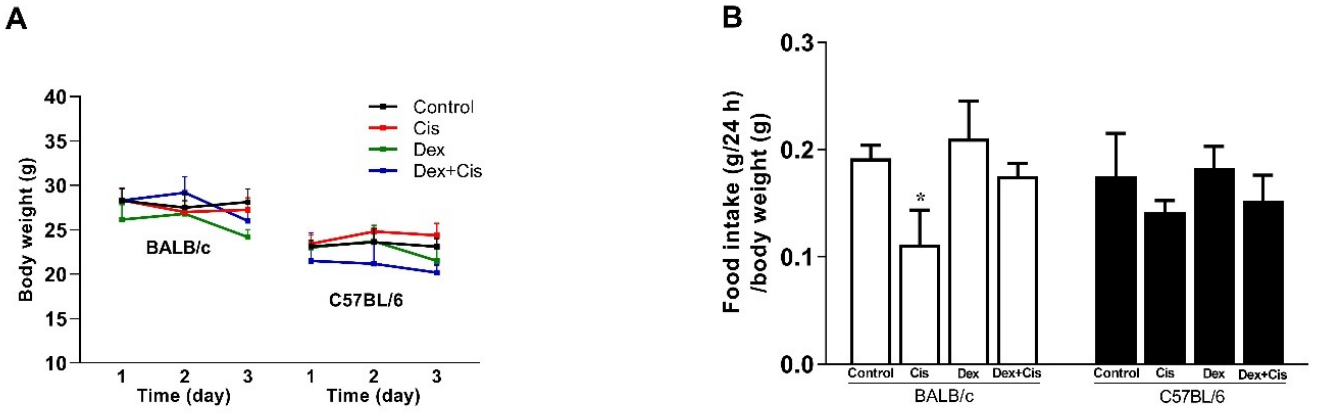

FIGURE 2 - Body weight (A) and Food intake relative normalized per gram body weight (B) in Control, Cis, Dex, and Dex+Cis groups in BALB/c and C57BL/6 mouse strains. *$p < 0.05$ vs Control group, indicate significant within-strain differences. The results are expressed as mean ± SD (n = 7). One-way ANOVA followed by Dunnet's post hoc test.

Figure 3 depicts the signals from gastric contractility registered in BALB/c and C57BL/6 mouse strains and their respective FFT spectrum. Gastric contractility was evaluated through the frequency and amplitude of contractions.

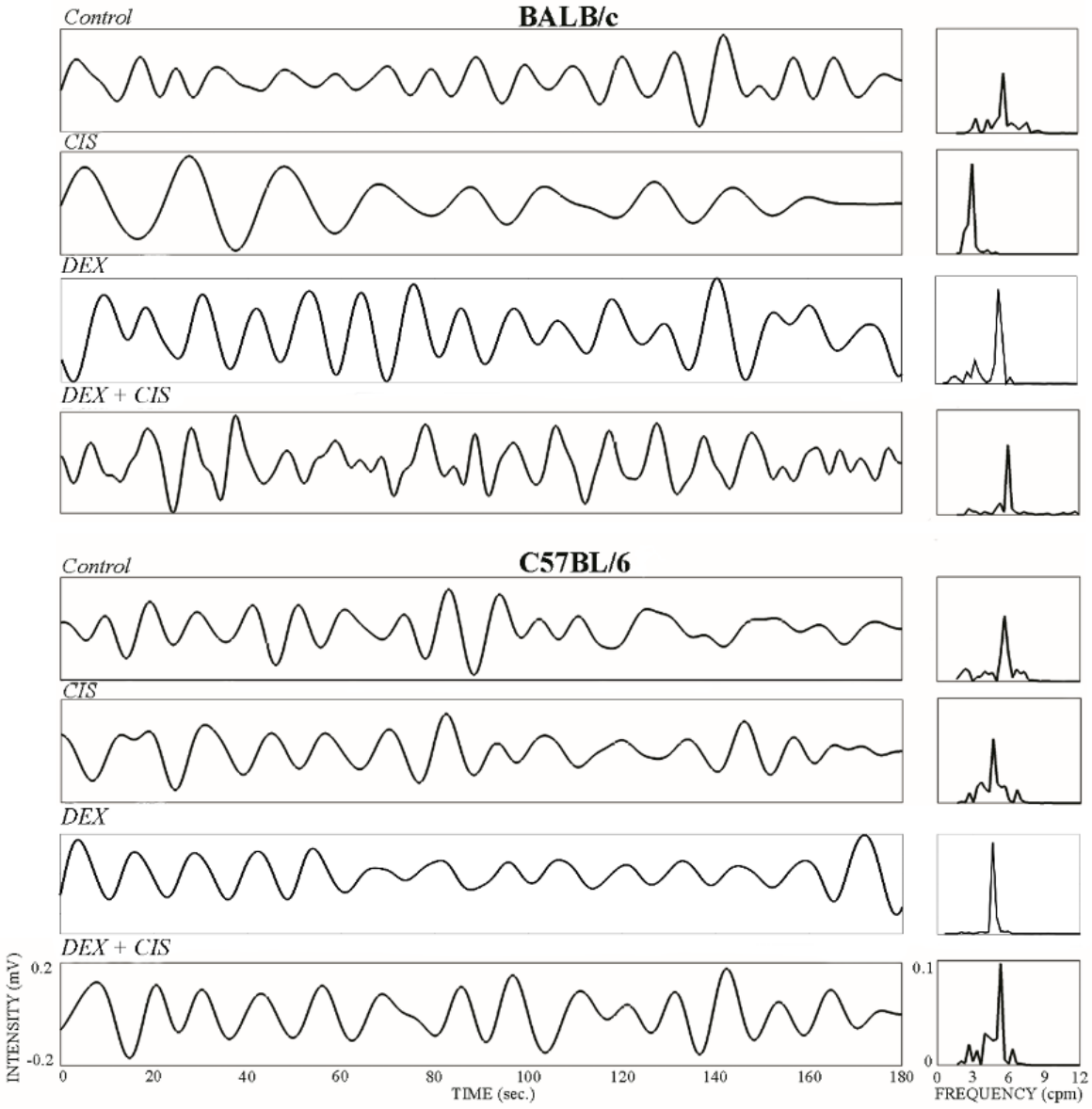

FIGURE 3 - Representatives of gastric contractility signals and their respective FFT spectrum obtained for Control, Cis, Dex, and Dex+Cis groups in BALB/c and C57BL/6 mouse strains.

In the BALB/c strain, the control group had a mean gastric frequency of 5.3 ± 0.5 cpm; normogastria was determined as frequencies ranging from 4.3 - 6.3 cpm. Similarly, in C57BL/6 mice, the control group had a mean gastric frequency of 5.4 ± 0.6 cpm; normogastria was determined as a range of frequencies between 4.2 - 6.6 cpm. Cisplatin reduced frequency of gastric contractions and caused bradygastria only in BALB/c (Figure 4A). Dexamethasone had no effect on the frequency of gastric contractions in BALB/c, but combined with cisplatin, prevented bradygastria caused by cisplatin. In C57BL/6 mice, the frequency of gastric contractions was not affected by any of the drugs administered isolated or in the combination.

Cisplatin reduced the amplitude of gastric contractions in both BALB/ and C57BL/6 (Figure 4B). Dexamethasone increased gastric amplitude only in BALB/c. Dexamethasone combined with cisplatin was not able to reverse the reduction in gastric amplitude caused by cisplatin on both mouse strains.

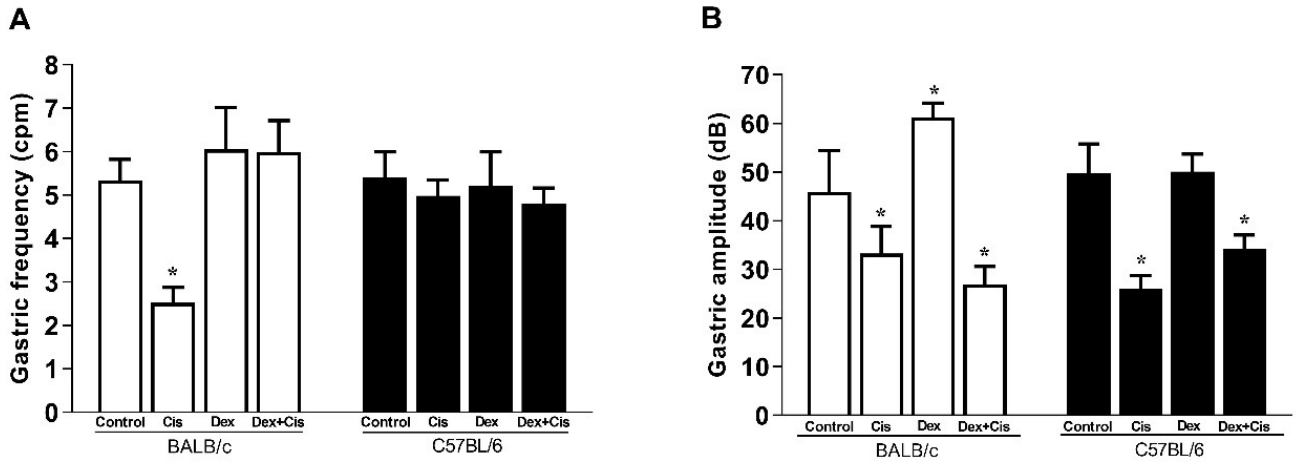

FIGURE 4 - Frequency (A) and amplitude (B) of gastric contractions in Control, Cis, Dex, and Dex+Cis groups quantified for both BALB/c and C57BL/6 strains. *p < 0.05 vs Control group, indicate significant within-strain differences. The results are expressed as mean ± SD (n = 7). One-way ANOVA followed by Dunnet's post hoc test.

Regarding the morphometric analysis, the thickness of the gastric mucosa was not affected by cisplatin alone or in association with dexamethasone for both strains (Figure 5A). Dexamethasone alone did not affect gastric mucosa thickness in BALB/c, but increased the mucosa thickness in C57BL/6. Cisplatin alone did not affect the thickness of the gastric muscular in BALB/c and C57LB/6 mice (Figure 5B). Dexamethasone administered alone decreased the gastric muscle layer in BALB/c; however, when combined with cisplatin, this effect does not exist. Gastric muscular thickness in C57BL/6 was not affected by dexamethasone alone or combined with cisplatin.

DISCUSSION

Our study showed that the administration of cisplatin and dexamethasone alone or in association results in disturbed gastric contractility and morphometric alterations in BALB/c and C57BL/6 mouse strains. These findings reinforce that the appropriate mouse strain is vitally important for safety and dose translation to clinical studies.

In our BALB/c and C57BL/6 mice, there were no significant changes in body weight after administration of cisplatin, as well as reported in previous studies (Aston *et al*., 2017; Yamamoto, Yamatodani, 2018). Cisplatin alone reduced the relative food intake in the BALB/c but did not affect C57BL/6 strain. Studies showed that cisplatin reduced food intake in C57BL/6 mice dose-dependently, whereas it remained constant in BALB/c (Liu *et al*., 2005; Holland *et al*., 2014; Yamamoto, Yamatodani, 2018). Dexamethasone combined with cisplatin avoids food intake reduction in BALB/c mice. It has already been demonstrated that Dexamethasone is able to inhibit cisplatin-induced anorexia in DBA mouse strain (Yamamoto, Yamatodani, 2018).

Although symptoms such as nausea and vomiting are often related to gastric disorders, the mechanisms triggered by drugs are not fully understood (Pini *et al*., 2016). Changes in gastric motility entail changes in frequency and/or in amplitude of contractions (Jin *et al*., 2020). Our data depicted that gastric frequency and amplitude were similar for both strains at the baseline, but BALB/c and C57BL/6 respond differently to the drugs administered. Cisplatin decreased the frequency of gastric contractions and caused a bradygastric pattern only in the BALB/c strain. The amplitude of contractions, in turn, was decreased in both BALB/c and C57BL/6 mice. Similarly, studies performed in rats treated with cisplatin reported decreases in the frequency of slow waves associated with a delay of gastric emptying, as well as decreases in the frequency and amplitude of gastric

contractions (Gong *et al*., 2016; Liu *et al*., 2018; Guo *et al*., 2019). Shortened amplitude peaks from the slow wave imply reduced voltage-dependent activation of Ca^{2+} influx into smooth muscle cells, with consequent diminished contractile activity (Izbeki *et al*., 2010).

Acute or chronic cisplatin administration in rats may be associated with gastric dysmotility and other symptoms related to decreased meal ingestion (Cabezos *et al*., 2008). Our results showed a decrease in food intake parallels to bradygastria and decreased amplitude in BALB/c treated with cisplatin. In C57BL/6, only the amplitude of contractions was reduced by cisplatin. It is important to highlight that food intake and gastric contractility was evaluated in an acute phase -response and it is possible that the C57BL/6 response to cisplatin is delayed, denoting a limitation of this study.

Regarding the morphometric analysis, cisplatin alone or in combination with dexamethasone did not affect the thickness of the gastric mucosa and muscle layers in both strains. Indeed, cisplatin causes damage to the gastrointestinal mucosa along the whole gastrointestinal tract in a dose and time-dependent manner (Perše, 2021). The absence of morphometric alterations in our study may be related to the short time of the experimental protocol. A previous study showed that 4 weeks of treatment with cisplatin resulted in gastric distension and neuropathy

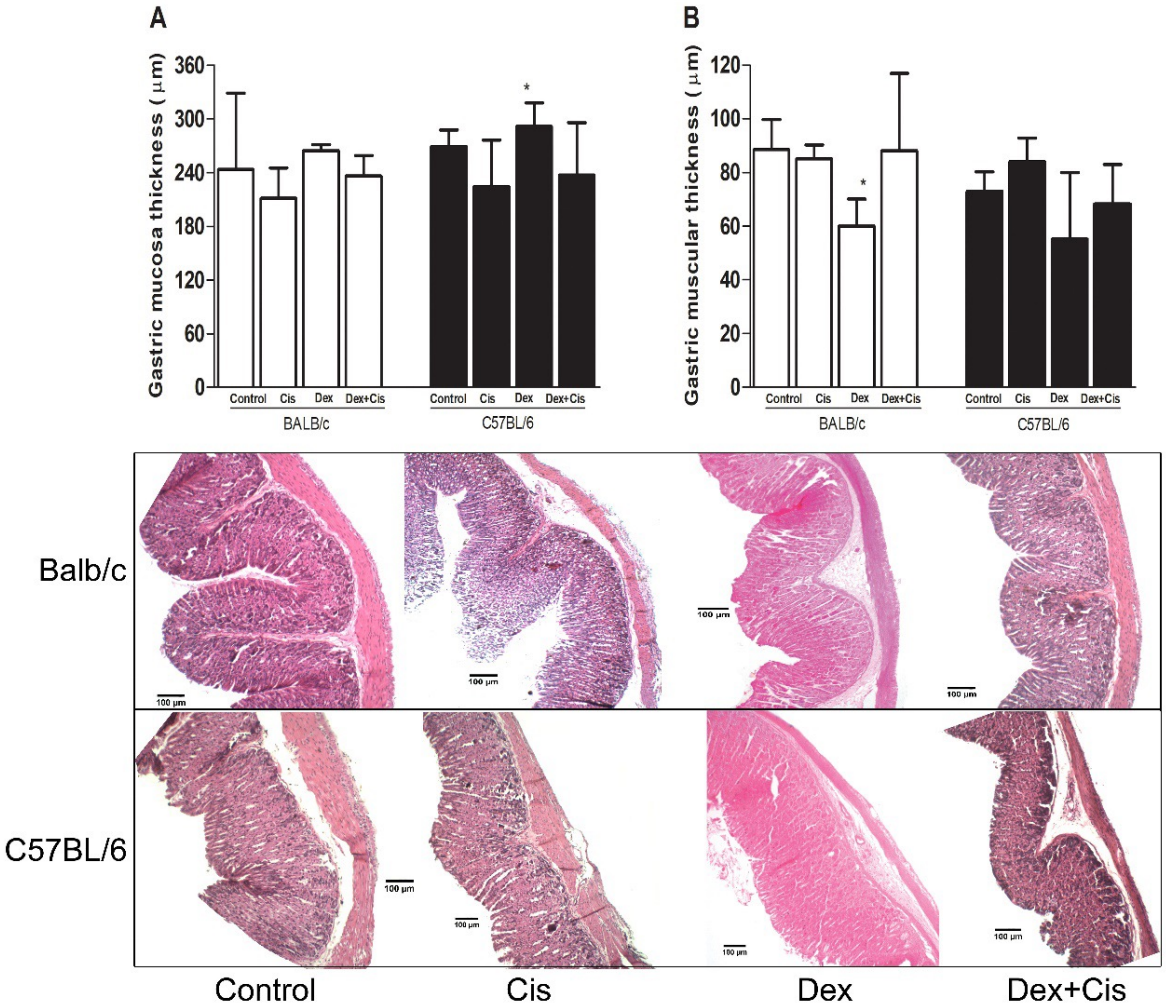

FIGURE 5 - Histomorphometry of gastric mucosa and muscular and in Control, Cis, Dex and Dex+Cis groups in BALB/c and C57BL/6 mouse strains are shown at the top of the panel. Representative photomicrographs of HE stained sections of stomachs of BALB/c and C57BL/6 mouse strains are shown at the bottom of the panel (original magnification ×10). *$p < 0.05$ vs Control group, indicate significant within-strain differences. The results are expressed as median ± range (n=7). Kruskal-Wallis's test followed by the Dunn's test.

besides a significant decrease in the thickness of gastric mucosa in C57BL/6 mice (Pini *et al*., 2016).

It is important to underline the range of adverse effects associated with corticosteroids in the GI tract even when used as an antiemetic, as this may correlated with the symptoms (Vardy *et al*., 2006). Our data pointed out that dexamethasone combined with cisplatin prevented bradygastric and, consequently, the decrease of food intake in BALB/c mice. Similarly, the administration of dexamethasone to cisplatin-treated rats inhibited pica, improved food intake, and reduced the weight of gastric content (Rudd *et al*., 2002; Malik *et al*., 2007; Obara *et al*., 2018). This effect may be connected to the inhibition of the production of inflammatory mediators (Plata-Salamán, 1991; Obara *et al*., 2018) and also to the increased transmembrane Ca^{2+} influx in smooth muscle cells generated for glucocorticoids, as seen in vascular smooth muscle in rabbits (Kornel *et al*., 1995). Conversely, the decrease in gastric amplitude of contractions was not prevented by the combination of dexamethasone and cisplatin in both BALB/c and C57BL/6 mice, suggesting that this gastric variable seems to be disturbed by different pathways in acute treatment.

Studies focused on gastrointestinal toxicity induced by cisplatin or on the investigation of gastroprotective strategies are scant (Shahid, Farooqui, Khan, 2018). Similarly, there are few studies underline on gastric function in mice presumably due to model or methodology limitations. Conflicting results regarding the effects of drugs may be a result of differences in dose, route and period of treatment, and animal model as well. It seems worthwhile noting that a study into 17 different mouse genomes, including classical laboratory strains and the progenitors of strains linked to over 5000 different types of knockout mice, identified 56.7 million unique single-nucleotide polymorphisms, 8.8 million unique indels and 0.28 million structural variants (Keane *et al*., 2011). Acute administration of cisplatin alone seems to lead to fewer changes on C57BL/6. In the study of Aston et al. (2017), the effects of dexamethasone combined with cisplatin showed a dose-dependent profile on weight loss, where the optimum dosage of dexamethasone is up to 0.2 mg/kg to avoid loss of body mass. In this study, the gastrointestinal tract was not evaluated. In our study, the dose of dexamethasone used was 2.0 mg/kg according to Malik et al. (2007), which demonstrated effects on the stomach. Dosage adopted may have contributed to the increase in the thickness of the gastric mucosa in C57BL/6 and the reduced thickness of the gastric muscle in BALB/c.

In terms of side effect of drugs on gastrointestinal function, the ACB technique proved to be suitable to evaluate the differences in the duodenal contractility, and gastrointestinal transit between BALB/c and C57BL/6 mouse strains (Gama *et al*., 2020). Nevertheless, the mechanisms contributing to differences in the physiology of the stomach between BALB/c and C57BL/6 mice require further study.

BALB/c and C57BL/6 mice showed a similar baseline, but the acute effect of cisplatin and dexamethasone alone or combined on the food intake, gastric morphometry and contractility were influenced by the strain. In conclusion, our results reinforce the importance of choosing the appropriate mouse strain for studying the acute effects of anticancer and protective drugs on the gastrointestinal tract.

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DECLARATION OF COMPETING INTEREST

The authors declare no conflict of interest.

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