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(p-ClPhSe)$_2$ stabilizes metabolic function in a rat model of neuroendocrine obesity induced by monosodium glutamate

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ABSTRACT

Obesity is a chronic and complex medical condition characterized by excessive fat accumulation and its complications include metabolic syndrome, diabetes and chronic inflammation. The aim of this study was to expand the knowledge about p-chloro-diphenyl diselenide (p-ClPhSe)$_2$ effects on enzymes and proteins involved in the metabolism of lipids and carbohydrates in a model of neuroendocrine obesity induced by MSG. Male Wistar rats were treated during the first ten postnatal days with MSG (4 g/kg, s.c.) and received (p-ClPhSe)$_2$ (10 mg/kg, i.g.) from 90th to 97th postnatal day. The hypothalamic function, insulin resistance and other biochemical parameters were determined in the rat blood, liver and skeletal muscle. The MSG administration induced hypothalamic neurotoxicity accompanied by metabolic disorders, including obesity, a transient insulin resistance, and metabolic alterations, demonstrated in the blood, liver and skeletal muscle, and lipotoxicity, characterized in the liver and skeletal muscle. The metabolic disorders in the liver and skeletal muscle were accompanied by the decrease in AMPK phosphorylation and activation of Akt. (p-ClPhSe)$_2$ restored most of metabolic parameters altered by MSG administration in rats. The hypothalamic neurotoxicity induced by MSG was accompanied by metabolic disorders in rats, which were regulated by (p-ClPhSe)$_2$.

1. Introduction

Statistical data show that obesity affects more than 300 million humans worldwide and projections for the next 20 years predict a global prevalence of up to 20% of obese individuals (Shaw et al., 2010). Obesity is a chronic and complex medical condition characterized by excessive fat accumulation and its complications include metabolic syndrome, diabetes and chronic inflammation (Debnath et al., 2016; Shaw et al., 2010).

During obese condition, the excess consumption of nutrients stimulates the inflammatory process damaging the metabolic homeostasis, not only in the adipose tissue but also in the liver, pancreas, brain and muscles (Debnath et al., 2016). Moreover, obesity is associated with the secretion of pro-inflammatory cytokines from adipose tissue, which could affect and compromise other tissues and mediate the cascade of events leading to insulin resistance (Araujo et al., 2016a; Cesar and Pisani, 2016).

It is known that insulin sensitivity and resistance depend on the specific kinases, such as AMP-activated protein kinase (AMPK), which acts on the insulin receptor substrate and activates the insulin signaling (Nandipati et al., 2017). AMPK is considered a positive regulator of metabolic homeostasis, which stimulates glucose uptake and glucose transporter 4 (GLUT4) translocation, reducing the phosphorylation of mammalian target of rapamycin (mTOR) (Garcia and Shaw, 2017). mTOR signaling has been implicated in the pathogenesis of obesity and the development of insulin resistance, besides stimulates the activation of NfκB pathway, contributes to the development of inflammatory process (Haissaguerre et al., 2014).

Furthermore, in animal models of obesity, it has been demonstrated the association between AMPK inhibition and fat accumulation in rats treated with subcutaneous neonatal monosodium glutamate (MSG) injections (Araujo et al., 2016b). There is a consensus that MSG administration induces a neuroendocrine obesity through hypothalamic lesion resulting in metabolic dysfunctions, weight gain, insulin resistance and chronic inflammation (Gobel et al., 2017; Miranda et al., 2016).

Selenium (Se) is an essential trace element that plays a crucial role in human health with special focus on its role in immune-endocrine pathophysiology, metabolism and inflammation process (Duntas and Benvenga, 2015). Regarding organoselenium compounds, a number of pharmacological actions, such as antihyperglycemic (Quines et al.,

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Abbreviations

(*p*-ClPhSe)$_2$	*p*-Chlorodiphenyl diselenide
Akt	Protein kinase B
ALT	Alanine aminotransferase
AMPK	AMP-activated protein kinase
AST	Aspartate aminotransferase
AUC	Area under the curve
CS	Citrate synthase
ERK	Extracellular signal–regulated kinases
FA	Fatty acids
G	Glucose
G6P	Glucose 6-phosphate
G-6-Pase	Glucose-6-phosphatase
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GLUT2	Glucose transporter 2
GLUT4	Glucose transporter 4
GR	Glucocorticoid receptor
HbA1c	Glycated hemoglobin
HPA axis	Hypothalamic pituitary adrenal axis
IDH	Isocitrate dehydrogenase
ITT	Insulin tolerance test
MAPK	Mitogen-activated protein kinase
MSG	Monosodium glutamate
mTOR	Mammalian target of rapamycin
NfκB	Nuclear factor kappa of activated B
NPY	Neuropeptide Y
OGTT	Oral glucose tolerance test
PKC	Protein kinase C
Se	Selenium
TAT	Tyrosine aminotransferase
TG	Triglycerides

2017; Ribeiro et al., 2013), antioxidant (Bortolatto et al., 2013), anti-inflammatory (Bruning et al., 2015), anorexigenic-like (Bortolatto et al., 2015) and neuroprotective (Zborowski et al., 2016), have been already demonstrated. Moreover, our research group showed that *p*-chlorodiphenyl diselenide (*p*-ClPhSe)$_2$ elicits a homeostatic effect in a model of obesity induced by MSG, regulating the activities of enzymes involved in the glucose metabolism (Quines et al., 2016).

Considering what was mentioned before, the aim of this study was to expand the knowledge about (*p*-ClPhSe)$_2$ effects on specific enzymes and proteins involved in the metabolism of lipids and carbohydrates in a model of neuroendocrine obesity induced by MSG in rats.

2. Materials and methods

2.1. Animals

The experiments were carried out using newborn Wistar rats from our own breeding colony. The animals were kept in a separate animal room, on a 12-h light/12-h dark cycle, the lights were turned on at 7:00 a.m., in a controlled temperature environment (22 ± 1 °C). Animals had free access to tap water and food. The experiments were performed according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, the Federal University of Santa Maria, Brazil (031/2014). All efforts were made to minimize animal suffering and to reduce the number of animals used in the experiments.

2.2. Drugs

(*p*-ClPhSe)$_2$ was prepared according to the method described previously (Paulmier, 1986). The chemical purity (99.9%) of (*p*-ClPhSe)$_2$ was determined by gas chromatography–mass spectrometry (GC/MS). ^{1}H and ^{13}C Nuclear Magnetic Resonance Spectroscopy analysis showed analytical and spectroscopic agreement with the assigned structure. (*p*-ClPhSe)$_2$ was diluted in mineral oil.

Monosodium glutamate (MSG) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Saline solution was used as a vehicle for MSG. All other chemicals were of analytical grade and obtained from standard commercial suppliers.

2.3. Experimental procedure

In order to induce obesity, newborn male rats (n = 116) were randomly assigned to two experimental groups (n = 58 each group), saline and MSG-treated groups. During the first ten days of life, the rats received MSG (4 g/kg body weight per day) or saline solution 0.9% (1 mL/kg) by the subcutaneous (s.c.) route (Klingberg et al., 1987). Rats were weaned at the 21st postnatal day. Furthermore, during the development of these animals, the Lee index was recorded by measuring the body weight and nasal-anal length at 30th, 60th and 90th days, to evaluate the grown performance of the rats and the development of obesity. Lee indices of the animals (saline and MSG groups) were calculated by $\frac{\sqrt[3]{body\ weigth\ (g)}}{nasal-anal\ length\ (cm)}$, rats with Lee index of 0.3 or more were considered obese (Bernardis and Patterson, 1968). At 60th postnatal day, the biochemistry parameters (glucose, triglycerides and cholesterol levels) were determined in samples of blood collected from the tail vein to monitor the development of metabolic disorders. At 90th day, the animals were assigned to four experimental groups: I - Control (saline + mineral oil n = 29); II - (*p*-ClPhSe)$_2$ (saline + (*p*-ClPhSe)$_2$

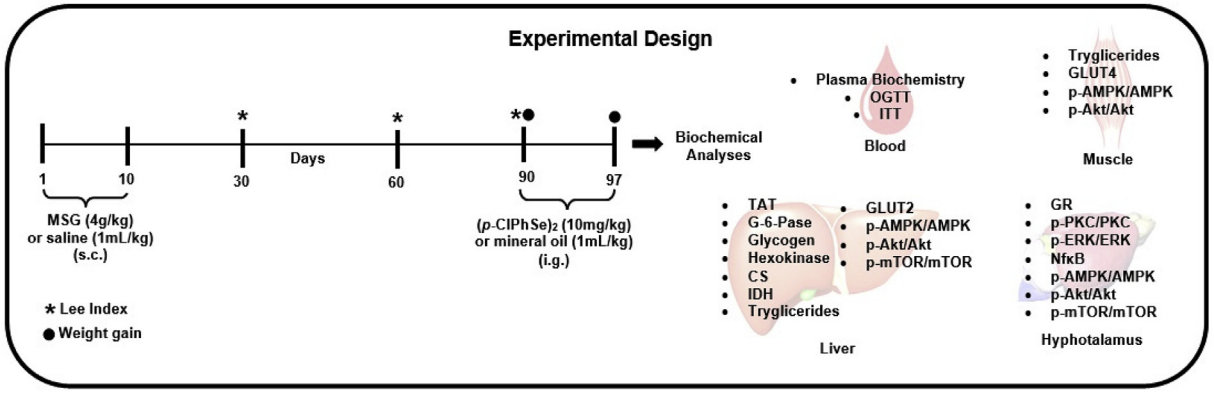

Fig. 1. Schematic representation of the experimental design of this study. MSG-monosodium glutamate; OGTT-oral glucose tolerance test; ITT-insulin tolerance test; TAT-tyrosine aminotransferase; CS-citrate synthase; IDH-isocitrate dehydrogenase; G-6-Pase-Glucose-6-phosphatase; GR-glucocorticoid receptor.