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ORIGINAL ARTICLE

Effect of N-acetylcysteine on mitochondria isolated from the rat kidney exposed to an iodinated radiographic contrast agent

Efeito da N-acetilcisteína em mitocôndrias isoladas de rins de ratos expostos a contraste radiológico

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Abstract

Background: Contrast-induced nephropathy (CIN) is an acute complication associated with iodinated radiographic contrast agents injected intravenously and is the third most common cause of hospital-acquired acute renal failure. Although some risk factors and preventive measures have been identified, the pathophysiology of CIN has yet to be completely clarified and studies have been conducted to investigate more effective preventive strategies. N-acetylcysteine (NAC), an antioxidant agent, has often been used to prevent CIN; however, reports on its efficacy are conflicting. Mitochondria are organelles whose predominant function is to generate ATP through oxidative phosphorylation. In the kidney, mitochondrial dysfunction has been associated with acute and chronic ischemic and nephrotoxic injury. Assessing mitochondrial dysfunction may help identify cell lesions at an early stage. The aim of the present study is to investigate the effect of NAC on oxygen consumption in mitochondria isolated from rat kidneys exposed to a radiographic contrast agent. **Methods:** Four groups of Wistar rats were evaluated including a control group (Group 1: untreated controls) and three experimental groups (Groups 2-4). The experimental groups were injected intraperitoneally with: 5 mL/kg of body weight of iobitridol (300 mg/mL) (Group 2); NAC (100 mL/kg at 24, 12 and 2 hours prior to saline infusion) (Group 3); and NAC (100 mL/kg at 24, 12 and 2 hours) prior to an infusion of 300 mg/mL of iobitridol (Group 4). Fifteen to twenty minutes after the intraperitoneal infusion of the contrast agent or saline, all the animals were sacrificed and their kidneys were collected individually, homogenized and submitted to differential centrifugation. Oxygen consumption was measured polarographically in the sediment containing principally mitochondria. **Results**: Mean oxygen consumption was 14.8% higher in the group exposed to iobitridol compared to the control group. Pre-treatment with NAC before the iobitridol infusion inhibited the increase in mean oxygen consumption ($p<0.05$). There were no significant differences in the endogenous respiration of mitochondria isolated from kidneys in the control group compared to the groups treated with NAC ($p>0.05$). **Conclusion:** The findings of the present study confirm a certain protective effect of NAC in rat kidneys exposed to an iodinated radiographic contrast medium.

Keywords: N-acetylcysteine. Mitochondria. Radiocontrast iobitridol. Nephropathy.

Resumo

Introdução: A nefropatia induzida por contraste (NIC) é uma complicação relacionada ao contraste radiológico iodado via endovenosa e é a terceira causa mais comum de internações hospitales por lesão renal aguda. Apesar de identificados alguns fatores de risco e algumas medidas preventivas, a fisiopatologia da NIC ainda não foi completamente esclarecida e estudos têm sido realizados para investigar estratégias preventivas mais eficazes. N-acetilcisteína (NAC), é um agente antioxidante que tem sido usado frequentemente na prevenção da NIC, embora os resultados dos estudos publicados tenham demonstrado eficácia não consistente. As mitocôndrias são organelas cuja função predominante é a geração de ATP através da fosforilação oxidativa. No rim, a disfunção mitocondrial tem sido associada com isquemia crônica e aguda e nefrotoxidade adquirida. Avaliando a disfunção mitocondrial pode ajudar a identificar lesões de células em um estágio inicial. O objetivo do presente estudo foi investigar o efeito da NAC sobre o consumo de oxigênio mitocondrial em rins de ratos expostos a contraste radiológico. **Métodos**: Foram estudados quatro grupos de ratos Wistar, incluindo o grupo controle (Grupo 1: animais controle) e 3 grupos experimentais (Grupo 2-4). Os grupos experimentais foram inoculados intraperitonealmente com: 5 ml/kg de peso corporal de iobitridol (300 mg/mL) (Grupo 2); NAC (100 mL/kg em 24 horas, 12 horas e 2 horas antes da infusão de solução salina) (Grupo 3); e NAC (100 mL/kg de peso corporal, em 24h, 12h e 2 horas) antes da infusão de 300 mg/mL iobitridol (Grupo 4). Quinze a vinte minutos depois da infusão intraperitoneal do contraste ou salina, todos os animais foram sacrificados e seus rins foram coletados individualmente, homogeneizados e submetidos à centrifugações diferenciadas. O consumo de oxigênio foi medido polarograficamente no sedimento contendo principalmente mitocôndrias. **Resultados**: A média de consumo de oxigênio foi de 14,8% superior no grupo exposto ao iobitridol que o grupo controle. O tratamento com NAC antes da infusão do iobitridol inibiu o aumento no consumo de oxigênio significativo ($p<0,05$). Não houve diferença significante na respiração endógena das mitocôndrias isoladas dos rins do grupo controle e dos grupos tratados com NAC ($p>0,05$). **Conclusão**: Os achados do presente estudo são consistentes com algum efeito protetor da NAC nos rins de ratos expostos ao contraste radio iodo.

Palavras-chave: N-acetilcisteína. Mitocôndria. Contraste iobitridol. Nefropatia.

INTRODUCTION

Contrast-induced nephropathy (CIN) is an acute complication of the exposure to iodinated radiographic contrast media administered intravenously[1]. CIN is the third most common cause of hospital-acquired acute renal failure, accounting for 10-13% of cases, and is associated with longer hospital stay and higher healthcare costs as well as higher morbidity and

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mortality rates[2,3]. Although some risk factors and preventive measures have been identified, the pathophysiology of CIN remains to be completely clarified[4].

Strategies aimed at preventing CIN involve hydration and the volume and osmolality of the contrast media[4,5]. Some pharmacological agents have been evaluated; however, no clear benefit has so far been shown[6,7]. N-acetylcysteine (NAC), an antioxidant, has often been used in an attempt to prevent CIN; however, the reports to date are inconsistent regarding the efficacy of this treatment[8-12].

Mitochondria are organelles whose predominant function is to generate ATP by oxidative phosphorylation; however, they are also involved in the synthesis of reactive oxygen species, in the regulation of cytoplasmic and mitochondrial matrix calcium levels and signaling, and in necrotic and apoptotic cell death1[3-15]. Mitochondrial dysfunction is associated with several diseases in humans[16]. In the kidney, mitochondrial dysfunction has been associated with acute and chronic ischemic and nephrotoxic injury[17-19]. The assessment of mitochondrial dysfunction may enable cell lesions to be identified at an early stage[20].

The objective of the present study was to investigate the effect of NAC on oxygen consumption in mitochondria isolated from the rat kidney exposed to a radiographic contrast medium.

METHODS

The internal review board of the Bahia School of Medicine and Public Health approved the study (protocol number 27/12) in December 2012. All experiments were conducted according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals. Four groups of 10 male Wistar rats (School of Veterinary Medicine, Federal University of Bahia), weighing 250 - 300 grams, kept in separate cages at a temperature of 21oC and in natural lighting, and fed with standard rat chow and tap water ad libitum, were studied as follows:

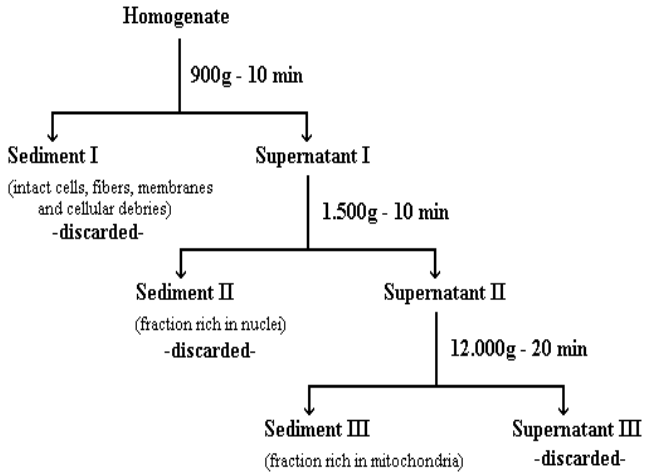
- **Group 1**: Untreated controls.
- **Group 2**: Rats were injected intraperitoneally with 5 mL/kg of body weight of iobitridol (300 mg/mL) over a period of 2 to 3 minutes. Iobitridol is a non-ionic, monomeric, low-osmolality radiographic contrast agent.
- **Group 3**: Animals were injected intraperitoneally with 100 mL/kg of body weight of N-acetylcysteine at 24, 12 and 2 hours prior to receiving an infusion of saline at a volume similar to the volume of the contrast agent used in Group 2.
- **Group 4**: The animals were injected intraperitoneally with 100 mL/kg of body weight of N-acetylcysteine at 24, 12 and 2 hours prior to receiving an infusion of iobitridol (300 mg/mL).

In the present experiments, the dose of NAC used was the same as that established by Conesa et al[21].

Fifteen to twenty minutes after the intraperitoneal infusion of the contrast agent or saline solution, each animal was sacrificed by cervical dislocation. In order to avoid any effect on mitochondrial activity, no anesthesia was used. Immediately after sacrifice, the kidneys were collected, identified and washed in 25 x 10^{-2}M saccharose solution at pH 7.4 and refrigerated at a temperature of 2-4°C. They were then reduced to small fragments, washed once again in the saccharose solution and suspended in a proportion of 1g of tissue to 10 mL of a special buffer solution (phosphate buffer 10^{-2}M, sodium chloride 2x10^{-3} M, TRIS 2x10^{-3M}, EDTA 4x1^{0-4}M and D-mannitol 25x10^{-2}M, adjusted to pH 7.4) to preserve the mitochondria.

The samples were then homogenized by using a Potter Elvehjem tissue grinder with a PTFE pestle at 250 rpm for a maximum of two minutes. The homogenates were subjected to differential centrifugation at 2°C (Figure 1) to isolate the subcellular fraction rich in mitochondria[22].

Figure 1. Schematic illustration of the refrigerated centrifugation used to separate the mitochondria-rich fraction



The sediment containing chiefly mitochondria was washed twice in the same buffer solution and then suspended at 2°C by adding the same volume of buffered solution that was used for the original homogenate. Oxygen consumption was measured polarographically at 37°C using a Clark electrode (YSI 5300A Biological Oxygen Monitor, Yellow Springs, OH, USA) in a solution containing 2.8 mL of the mitochondrial homogenate and 0.2 mL of sodium succinate 3.3 x 10-3 M[22-24]. The amount of total protein in each sample was determined by using a modification of the Folin-biuret technique[25].

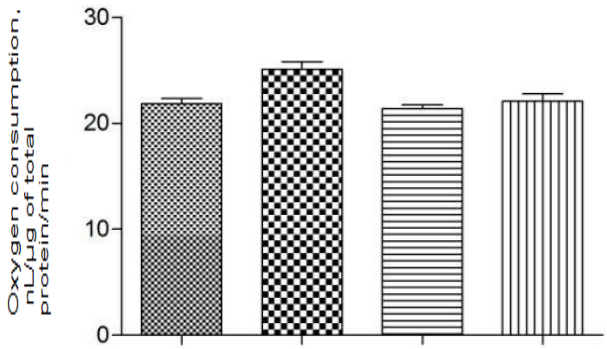
The data were expressed as means ± standard deviations (SD). Comparisons between groups were performed using analysis of variation (ANOVA). P-values <0.05 were considered statistically significant. The entire statistical analysis was performed using the GraphPad Prism software program, version 3.0 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

The endogenous respiration of mitochondria isolated from kidneys in the four groups of animals is shown in Figure 2 and

is expressed as mean oxygen consumption in nL per µg of total protein per minute.

Figure 2. Endogenous mitochondrial respiration in the four experimental groups



I. Oxygen consumed by mitochondria isolated from kidneys of rats in the control group (mean and standard deviation).
II. Oxygen consumed by mitochondria isolated from kidneys of rats in the group treated with the contrast medium iobitridol.
III. Oxygen consumed by mitochondria isolated from kidneys of rats in the group treated with N-acetylcysteine and then with saline.
IV. Oxygen consumed by mitochondria isolated from kidneys of rats in the group treated with N-acetylcysteine and then with iobitridol.

Mean oxygen consumption was 14.8% higher in the group exposed to iobitridol compared to the control group (25.12 ± 2.2 and 21.87 ± 1.6 nL respectively, $p<0.05$). Treatment with NAC prior to the iobitridol infusion (Group 4) inhibited the increase in mean oxygen consumption ($p<0.05$). There were no statistically significant differences in the endogenous respiration of mitochondria isolated from the kidneys of animals in the control group compared to the NAC-treated groups (Groups 3 and 4) (21.87 ± 1.6, 21.4 ±1.0 and 21.87 ± 1.6 9 nL of oxygen consumption per µg of total protein per minute of experiment, respectively).

DISCUSSION

NAC, chemical formula C5H9NO3S and molecular weight 163.2 Da, is a sulfhydryl-containing acetylated derivative of the amino-acid cysteine with antioxidant properties[8,26]. Although NAC neutralizes certain free radicals in vitro, it is believed that, in vivo, its antioxidant effects would be indirect, through induction of glutathione synthesis[26,27]. In addition, NAC has a vasodilator effect by stabilizing nitric oxide and inhibiting angiotensin-converting enzymes[27-32].

Although the pathophysiology of CIN has yet to be completely understood, vasoconstriction, hypo-perfusion with the production of reactive oxygen species and direct cytotoxicity are factors known to be involved in the kidney lesion associated with radiographic contrast media[4,33-35]. In view of its biological effects, NAC might be an important pharmacological agent for the prevention of CIN.

The findings of the present study show a certain protective effect of N-acetylcysteine in the kidneys of animals exposed to an iodinated radiographic contrast agent, as shown by mitochondrial oxygen consumption. In fact, the specific respiratory coefficient (measured as nanoliters of oxygen consumed per microgram of total protein per minute) in the kidneys of animals exposed to the radio contrast agent could be related to the iodine ions in the contrast medium. It is known that iodine-substituted benzene derivatives such as radio contrast agents and thyroxin-like analogs uncouple oxidative phosphorylation and increase the mitochondrial respiratory chain[36,37]. Oxygen consumption was similar in the controls and in the NAC-treated groups. The finding that NAC prevented the increase in oxygen consumption in animals exposed to the contrast medium compared to the animals exposed to the contrast medium alone without pretreatment with NAC is consistent with the theory that NAC exerts a certain protective effect on tubular cells exposed to iodinated radiographic contrast media.

Although there is a rationale for using NAC to prevent CIN, results from clinical trials have been inconclusive, with some studies reporting a protective effect, while others show no benefit. However, the heterogeneity of the results could be related to a publication bias, to inadequate sample sizes or even to the definitions used to describe acute kidney injury[38-40].

The findings of the present study are consistent with the theory that NAC exerts a protective effect on the rat kidney exposed to iodinated radiographic contrast media. However, in addition to being a laboratory study, the experiments were performed in apparently normal animals in which kidney function, vascular disease, diabetes mellitus, blood pressure levels and aging, to mention just some of the known risk factors for CIN, were not assessed[7].

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