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The effects of *N*-acetylcysteine on cisplatin-induced cardiotoxicity on isolated rat hearts after short-term global ischemia

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ABSTRACT

The aim of this study was to estimate the protective effect of *N*-acetyl-L-cysteine (NAC) against cisplatin-induced cardiotoxicity under conditions of ischemic-reperfusion injury.

Wistar albino rats were randomly divided into three groups ($n = 8$): control, cisplatin (5 mg/kg/w, i.p., 5 weeks) and cisplatin + NAC group (cisplatin – 5 mg/kg/w, i.p. and NAC – 500 mg/kg/w, i.p., 5 weeks). Isolated hearts were perfused according to the modified Langendorff technique at constant pressure (70 cmH_2O). Following cardiodynamic parameters were measured: maximum rate of left ventricular pressure development, minimum rate of left ventricular pressure development, left ventricular systolic pressure (SLVP), left ventricular diastolic pressure and heart rate. The ischemic vasodilation episodes were induced by the complete interruption of coronary inflow for 30, 60 and 120 s. The samples of the coronary venous effluent (CVE) were continuously collected during the reperfusion period for determination of coronary flow (CF) rate and oxidative stress markers (H_2O_2, O_2^-, NO_2^- and thiobarbituric acid reactive substances – TBARS).

Cisplatin reduced CF, heart rate and overflow (total, maximal and duration of overflow) during reperfusion, and increased SLVP (under basal conditions and after global ischemias). Cisplatin increased levels of H_2O_2 (under basal conditions), O_2^- and TBARS (under basal conditions and after ischemia), but decreased NO_2^- levels (during reperfusion) in CVE, and decreased superoxide dismutase and reduced glutathione in serum. NAC attenuated cisplatin-induced changes of cardiodynamic parameters (except CF under basal conditions) and oxidative stress parameters.

Those results suggest that NAC, by decreasing oxidative stress, may be useful in cardioprotection during cisplatin therapy.

1. Introduction

Since the accidental discovery four decades ago, cisplatin (*cis*-dichlorodiammine-platinum(II), CDDP) remained one of the most commonly used chemotherapeutic drugs. The effect of this anti-neoplastic agent has been demonstrated against various types of tumors, such as solid tumors and hematological malignancies, including testicular, ovarian, bladder, head and neck, esophageal, stomach and lung cancer, as well as lymphoma and osteosarcoma [7]. Mechanism of cisplatin action is achieved by interaction with DNA via formation of covalent adduct [56]. However, despite of its beneficial antitumor activity, cisplatin showed numerous adverse effects and toxicities affecting gastrointestinal, renal, neurological and hematological system, even when administered at standard doses [62]. Although statistically classified as rare, cardiotoxicity is one of the most serious side effects of cisplatin therapy described in numerous studies.

This cardiotoxic manifestations of cisplatin include electrocardiographic changes, arrhythmias, cardiomyopathy, congestive heart failure [70] and tromboembolic events [45]. Ischemia syndrome, palpitation and myocardial infarction can occur during treatment with cisplatin, or even as long-term consequences [57]. Treatment with cisplatin can be also associated with occasional

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