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Original Article

Inflammatory bowel and oxidative stress changes in an experimental model of portal hypertension: action of N-acetylcysteine

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ABSTRACT

Introduction: Portal hypertension (PH) is characterized by vasodilatation in the portal system and the bowel is one of the severely affected organs. N-acetylcysteine (NAC) is a molecule with important properties and widely used in clinical practice.
Objective: To evaluate NAC action in the bowel of animals submitted to the animal model of partial portal vein ligation (PPVL).
Methods: 18 male Wistar rats were divided into three experimental groups ($n=6$): sham-operated (SO), PPVL, and PPVL + NAC. On the 8th day after surgery, N-acetylcysteine (10 mg/kg, ip) was administered daily for 7 days. On the 15th day the animals' bowel was collected for oxidative stress analysis, immunohistochemistry and Western blot. We evaluated the expression of NF-KB and TNF-α by immunohistochemistry and of iNOS by Western blot. Lipid peroxidation was assessed by TBARS technique, and the activities of antioxidant enzymes superoxide dismutase (SOD) and glutation peroxidase (GPx) were checked.
Results: We observed an increased expression of NF-KB and TNF-α in PPVL group, and an increased iNOS expression assessed by Western blot. NAC reduced the expression of all proteins evaluated. We also observed an increase in oxidative stress in the bowel of mice PPVL group compared to controls (SO), and NAC was effective in reducing these values in PPVL + NAC group. Also, a reduction in the activity of SOD and GPx enzymes was observed in the diseased group, and NAC was able to restore the activity of the enzymes assessed.
Conclusion: We suggest the anti-inflammatory and antioxidant action of NAC in the bowel of animals submitted to PPVL model.

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Alterações intestinais inflamatórias e de estresse oxidativo em modelo experimental de hipertensão portal: ação da N-acetilcisteína

Palavras-chave:
N-Acetilcisteína
Hipertensão Portal
Intestino
Estresse Oxidativo
Inflamação

RESUMO

Introdução: A Hipertensão Portal (HP) é caracterizada por uma vasodilatação no sistema portal, e o intestino é um dos órgãos gravemente acometidos. A N-acetilcisteína (NAC) é uma molécula com importantes propriedades, amplamente utilizada na clínica.
Objetivo: Avaliar a ação da NAC no intestino de animais submetidos ao modelo animal de ligadura parcial da veia porta (LPVP).
Métodos: Foram utilizados 18 ratos machos Wistar divididos em três grupos experimentais (n = 6): Sham-operated (SO), LPVP, LPVP + NAC. No 8° dia após a cirurgia, a N-acetilcisteína (10 mg/kg,ip) foi administrada diariamente durante 7 dias. No 15° dia foi coletado o intestino dos animais para análises de estresse oxidativo, imunohistoquímica e Western blot. Nós avaliamos a expressão do NF-kb e TNF-α por imunohistoquímica e da iNOS por Western blot. A lipoperoxidação foi avaliada pela técnica de TBARS, e as atividades das enzimas antioxidantes Superóxido Dismutase (SOD) e GlutationaPeroxidase (GPx) foram verificadas.
Resultados: Observamos um aumento da expressão do NF-kb e TNF-α no grupo LPVP, e aumento na expressão da iNOS avaliada por Western blot. A NAC reduziu a expressão de todas as proteínas avaliadas. Observamos um aumento do estresse oxidativo no intestino dos ratos do grupo LPVP com relação aos controles (SO), sendo a NAC eficaz na redução desses valores no grupo LPVP + NAC. Ainda, uma redução na atividade das enzimas SOD e GPx no grupo doente, sendo a NAC capaz de restaurar a atividade das enzimas avaliadas.
Conclusão: Sugerimos a ação anti-inflamatória e antioxidante da NAC no intestino de animais submetidos ao modelo LPVP.

Introduction

Portal hypertension (PH) is a syndrome whose clinical picture is established by the emergence of an anatomical obstacle in the portal system. This obstacle, which blocks the blood flow, causes blood damming at the site of obstruction. The compensatory mechanism of decompression in the portal system is the development of an important vasodilation in the splanchnic territory; in turn, this event is responsible for the main complications of the portal hypertension syndrome.[1]

We can correlate the development of a hyperdynamic collateral circulation with one of the major complications from PH: the bleeding from gastrointestinal varices, an event that is triggered when the portal pressure gradient rises above 12 mmHg.[2] The progressive vasodilation in the splanchnic territory is responsible for the appearance of these varicose veins, the most important being those located in the stomach and bowel. These conditions are known as Portal Hypertension Gastropathy (PHG) and Portal Hypertensive Colopathy (PHC), respectively, and the first of these conditions is already well established in the literature.[3]

Intestinal changes present in PH are still being elucidated and were gradually identified over the last decade as being mainly one of the causes of fatal gastrointestinal bleeding in patients with PH.[4] The pattern of lesions in cases of PH can be found in other parts of the gastrointestinal tract, including the intestine,[5] due to mucosal edema, inflammatory diseases, and ectopic and anorectal varices.[6]

The experimental model of Partial Portal Vein Ligation (PPVL) has been used by many authors to study the molecular changes in pre-hepatic portal hypertension.[7–9] In rats, the hemodynamic changes present in PH show up around the day 14 after surgery, and hyperdynamic circulation and splanchnic vasodilation are prevailing conditions in animals subjected to a PPVL model.[10] In addition, PHC and encephalopathy are among the most important manifestations resulting from this experimental model, and inflammatory mechanisms are aggravating factors in both manifestations.[11]

Inflammation is an event often associated with injuries of different origins. In the case of PH, systemic and splanchnic vascular responses appear to play an important role in the pathogenesis of hyperdynamic circulation and are very similar to those produced in the post-traumatic inflammatory response. The mechanical stress caused by the increased blood flow in the splanchnic territory stimulates the endothelium to secrete vasoactive substances, cytokines and growth factors, and this is a triggering factor for local or generalized inflammation.[12]

With respect to local inflammation, it is important to mention that the mucosa of the gastrointestinal tract is a major reservoir of macrophages and mast cells, and these cells located in the intestine are considered as effector cells that participate in the first line of defense of our body.[13] In the case of inflammation, the intestinal mucosa acquires a phenotypic pro-inflammatory profile, secreting cytokines that can amplify the systemic inflammatory vascular response.[12]

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