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Comparative study of 1,2-dimethylhydrazine and azoxymethane on the induction of colorectal cancer in rats

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ABSTRACT

The induced colorectal carcinogenesis in rodents has a long history and currently uses the substances 1,2-dimethylhydrazine and azoxymethane.

Objective: The aim of this study was to compare the inductive effect of the substances azoxymethane and 1,2-dimethylhydrazine in colorectal carcinogenesis.

Method: 30 randomly chosen male Wistar rats were divided into four groups. G1 group was treated with 1,2-dimethylhydrazine and C1 was its control group; G2 group was treated azoxymethane and C2 was its control group. The animals were weekly weighed until euthanasia, when their intestines were removed, processed and analyzed by an experienced pathologist.

Results: Among the control groups (C1 and C2) no histologic changes were observed; moderate dysplasia was detected in G2 group; hyperplasia, mild dysplasia, severe dysplasia and carcinoma were observed in G1 group. When this study compared the cost of the substances, 1,2-dimethylhydrazine was more than 50 times less expensive than azoxymethane.

Conclusion: Azoxymethane is able to promote histological changes consistent with colorectal carcinogenesis. 1,2-Dimethylhydrazine produced neoplasia and dysplasia, and, compared to the azoxymethane, was more efficient in the induction of colorectal cancer.

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Estudo comparativo das substâncias 1,2-dimetil-hidrazina e azoximetano na indução de câncer colorretal em ratos

Palavras-chave:
Câncer colorretal
Modelo experimental
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RESUMO

A carcinogênese colorretal induzida em roedores tem longa história e utiliza, atualmente, as substâncias 1,2 dimetil-hidrazina (DMH) e azoximetano (AOM).

Objetivo: Comparar o efeito indutivo das substâncias AOM e DMH para o câncer colorretal (CCR).

Método: 30 ratos Wistar machos foram randomizados em quatro grupos. O grupo G1 foi inoculado com DMH, o grupo C1 foi seu controle; G2 recebeu o AOM e C2 foi seu controle. Os animais foram pesados semanalmente até a eutanásia, quando tiveram seus intestinos retirados, processados e analisados por um patologista experiente.

Resultados: Os animais dos grupos de controle apresentaram tecido colorretal normal e os animais do grupo G2 apresentaram um padrão de displasia moderada. Nas lâminas do grupo G1, foram encontradas regiões de hiperplasia, displasia leve, displasia grave, e carcinoma. Comparado o custo das substâncias AOM e DMH, este último teve um preço mais de 50 vezes menor ao do AOM.

Conclusão: AOM é capaz de promover alterações histológicas compatíveis com a carcinogênese colorretal. DMH produziu neoplasia e displasia grave e, comparada ao AOM, foi mais eficiente na indução do câncer colorretal.

Introduction

The number of new cases of colon and rectal cancer estimated for Brazil in 2012 is 30,140, with 14,180 in men and 15,960 in women.[1]

The etiology of colorectal cancer (CRC) is known to be multifactorial, including family, environmental and dietary agents. Despite many advances in our understanding of the processes of carcinogenesis, to date, therapies including surgery, radiation and chemotherapy drugs are still limited to treat advanced stages of CRC.[2–4] The only satisfactory answer to the problem of malignancy is its prevention. This involves an extensive search for acquiring knowledge of the basic aspects of carcinogenesis.[5,6]

The carcinogenesis and development of CRC are multistep processes, characterized by progressive changes in the amount or activity of proteins that regulate the proliferation, differentiation, and cell survival, and that are mediated by genetic mechanisms. An ordered sequence of non-random events leads to the development of colorectal cancer, with the epithelium undergoing an invasive transformation, with progression from normal intestinal epithelium to the development of invasive carcinoma.[5,7–12]

Animal models are good chances to study the biology of disease development. In addition, these models allow for testing hypotheses relating environmental factors to the etiology and prevention of cancer.[7]

The study of colorectal carcinogenesis in rodents has a long history, dating back approximately 80 years. Currently, experimental models use colorectal carcinogens 1,2-dimethylhydrazine (DMH) and azoxymethane (AOM).[13–16]

DMH falls in the category of an indirect inducer drug. This drug has the ability to promote DNA hypermethylation of colorectal epithelial cells in the segment. AOM is a derivative of dimethylhydrazine. However, unlike DMH, AOM falls under the category of a direct inducer, without relying on conversion in vivo.[17]

This study aims to compare the inductive effect of the substances AOM and DMH for colorectal carcinoma in an attempt to identify a more efficient animal model for the induction of CRC in rats.

Method

Animals

30 Wistar rats from the Central Animal Laboratory, Universidade Federal de Alagoas (UFAL), submitted to a light–dark cycle of 12 h, and fed with standard diet and water ad libitum, were used. The study was approved by the Ethics in Research Committee (ERC), Universidade Federal de Alagoas, and all experimental steps were performed in accordance with the principles established by the Colégio Brasileiro de Experimentação Animal (COBEA).

Experimental groups and technique

The animals were randomized into four groups: two groups of ten animals (G1 and G2) and two of five (C1 and C2). G1 was submitted to induction by DMH, and C1 was its control group. G2 received AOM and C2 was its control group.

DMH was administered dissolved in 0.9% NaCl containing 1.5% EDTA as a vehicle, adjusted to a final pH of 6.5 with 1 N NaOH solution and applied subcutaneously once a week for five weeks at a dose of 65 mg/kg/week.[18]