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Original Article

Effect of the combined administration of vitamin-E and 5-aminosalicylic acid on acrylamide-induced testicular toxicity

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الملخص

أهداف البحث: تهدف هذه الدراسة إلى التقييم المقارن للتأثير المضاد للأكسدة بين حمض ٥-أمينوساليسيليك وفيتامين "إي" في الحماية ضد تسمم خصى الفئران الناتج عن الأكريلاميد.

طرق البحث: أجريت هذه الدراسة في مركز الملك فهد للبحوث الطبية بجدة بالمملكة العربية السعودية. حيث تم تقسيم ما مجموعه ٤٩ من فئران ويستار البالغين (٢٥٠ ± ٢٠غم)، والبالغة من العمر ٦٠ يوما إلى سبع مجموعات؛ المجموعة الضابطة، ومجموعة الأكريلاميد وحدها، ومجموعة الأكريلاميد مع حمض ٥-أمينوساليسيليك، ومجموعة الأكريلاميد مع فيتامين إي، ومجموعة الأكريلاميد مع حمض ٥-أمينوساليسيليك وفيتامين إي، ومجموعة فيتامين إي وحدها، ومجموعة حمض ٥-أمينوساليسيليك وحده. أعطي الأكريلاميد (٤٥ ملغم/كغم من وزن الجسم يوميا) عن طريق الفم وفيتامين إي (٢٠٠ ملغم/كغم من وزن الجسم يوميا) عن طريق الفم، وتم حقن حمض ٥-أمينوساليسيليك (٢٥ ملغم/كغم من وزن الجسم يوميا) بالحقن داخل التجويف البريتوني لمدة خمسة أيام متتالية بعد يوم واحد من المراقبة. تم قتل الفئران عن طريق خلع فقرات العنق. ثم أجريت الفحوصات النسيجية المرضية على الخصى؛ وإنزيم "إليسا" المناعي المرتبط بالتستوستيرون، وفحص لاكتيت الاختزالي، وعد الحيوانات المنوية الذيلية.

النتائج: أظهرت الفئران التي عولجت بالأكريلاميد علامات العدوانية وخشونة الفروة مع انخفاض في استهلاك الماء والغذاء. كما أظهرت تغيرات نسيجية في صورة تساقط الغشاء السطحي للأنابيب المنوية داخل التجويف الأنبوبي مع عدم وجود الخلايا العملاقة متعددة النوى. كما لوحظ انكماش الأنابيب المنوية مع اتساع الفضاء الخلالي وضمور وسقوط الغشاء المخاطي الطبيعي. وأظهرت نتائجنا أن أقصى حماية نتجت عن محصلة الأثر المضاد للأكسدة الناتج عن فيتامين إي مع حمض ٥-أمينوساليسيليك على أنسجة الخصية.

الاستنتاجات: نستنتج أن الأكريلاميد يسبب تآكلا في القنوات المنوية وأن التآكل الذي يسببه الأكريلاميد يمكن عكسه جزئيا باستخدام حمض ٥-أمينوساليسيليك وفيتامين إي ونقترح التقليل من التعرض للأكريلاميد.

الكلمات المفتاحية: حمض ٥-أمينوساليسيليك؛ فيتامين إي؛ الأكريلاميد؛ ضمور الخصية؛ القنوات المنوية

Abstract

Objectives: This study aimed to evaluate the comparative protective antioxidant effect of 5-aminosalicylic acid (5-ASA) and vitamin-E against acrylamide (ACR)-induced testicular toxicity in rats.

Methods: This study was performed at King Fahad Medical Research Centre, Jeddah, KSA. A total of 49 adult Wistar rats (250 ± 20 gm) that were 60 days old were divided into seven groups (control, ACR alone, ACR + 5-ASA, ACR + Vitamin-E, ACR + 5-ASA + Vitamin-E, Vitamin-E alone, 5-ASA alone). Acrylamide [45 mg/kg (bw)/day] and vitamin-E [200 mg/kg (bw)/day] were gavaged orally, and 5-ASA [25 mg/kg (bw)/day] were injected intra-peritoneally for five consecutive days after one day of observation. Rats were sacrificed by cervical dislocation. Histopathology of the testis, enzyme linked immunosorbent assay (ELISA) of testosterone, the lactate dehydrogenase (LDH) assay and a caudal sperm count were performed.

Results: Rats treated with ACR showed signs of aggression and rough coats, with reduced food and water intake. ACR treated rats showed histopathological changes in the form of a sloughed seminiferous epithelium in the tubular lumen with no multinucleated giant cells. Shrinkage of seminiferous tubules with widening of the interstitial space was also observed with atrophy and the shedding of normal mucosa. Our results indicated

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that maximum protection was conveyed by the combined antioxidant effect of vitamin-E and 5-ASA on testicular histopathology.

Conclusion: We conclude that acrylamide-induced degeneration of seminiferous tubules can be partially reversed by the administration of 5-ASA and vitamin-E and suggests restricting exposure to ACR.

Keywords: 5-ASA; Acrylamide; Seminiferous tubules; Testicular atrophy; Vitamin-E

Introduction

Acrylamide (ACR) is a highly toxic chemical that is widely used in the manufacturing of polyacrylamides, which have a wide range of industrial applications, including the production of dyes, paper, plastics and the treatment of water. The workplace environment can be considered dangerous where exposure to acrylamide occurs via different routes, including direct contact with the toxic substance itself and inhalation through ACR contaminated airways.[1] Apart from occupational exposure, a major route of acrylamide toxicity to humans is via foods that are heated to temperatures above 120 °C.[2] ACR as a food toxicant is found in carbohydrate rich foods with low protein, including fried potatoes, potato chips, coffee and cereals that are cooked under high temperature where the Maillard reaction occurs between asparagine amino acids and glucose, producing acrylamide.[3,4] ACR was declared a "potential human carcinogen" in 1994 by the International Agency for Research on Cancer.[5] This finding was supported by the Scientific Committee on Toxicity, Ecotoxicity and the Environment by explaining its connate toxic nature with adverse effects on the skin, digestive system, circulation, respiratory system, endocrine system, nervous system and reproductive system, particularly the testicles, in addition to its harmful carcinogenic impact.[6,7] The chemical structure of acrylamide is shown in Figure 1.[8]

Once absorbed by the body, ACR is metabolized by either of two chief pathways: glutathione conjugation and glycidamide epoxidation.[9] It may either be conjugated by glutathione-S-transferase to N-acetyl cysteine or may react with cytochrome P2E1 (CYP2E1) to produce glycidamide.[9] The toxicity of ACR is credited to the fact that it can be bio-transformed to its highly active metabolite, glycidamide (GA). This pathway is regulated by the enzyme cytochrome P450 E1 (CYP2E1).[10,11] Glycidamide was found to be more harmful to deoxyribonucleic acid (DNA) and proteins compared to acrylamide.[12] The metabolism of ACR by CYP450 E1 leads to the formation of free radicals [reactive oxygen species (ROS)], consequently initiating oxidative stress and tipping the balance between the production and destruction of ROS, thus expediting lipid peroxidation and DNA and protein alterations.[13–15]

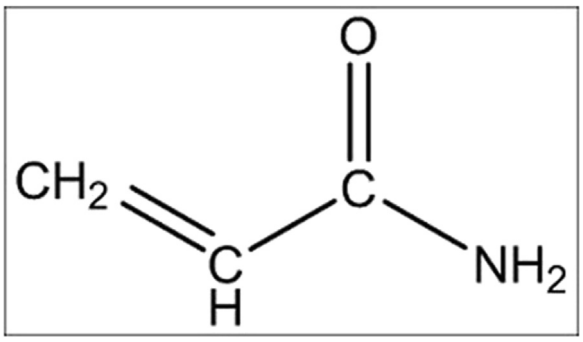

Figure 1: Chemical structure of acrylamide.

Thus, compounds showing antioxidative properties could be used as effective protective agents against ACR-induced toxicity. Vitamin-E is one such compound known for high antioxidant properties.[16,17] It has a high capacity for protection against free radical formation and can reduce peroxidative chain reactions.[18,19] Beyond its extensive role in the protection of vital tissues, vitamin-E has been shown to improve physiological function in rats with limited sperm motility.[20] Vitamin-E primarily scavenges free radicals out of the body to control cellular signalling and prompting gene expression.[21] Several hypotheses have been made with regards to the effectiveness of 5-aminosalicylic acid (5-ASA) against reactive oxygen species (ROS) formation. One study shows that it plays a dominant role as an antioxidant as well as an anti-inflammatory compound *in vivo*.[22] 5-ASA could be developed as a potential curative agent for ACR-induced renal toxicity, either in combination with vitamin-E or alone.[23] The protective effect of 5-ASA relies on the blockage of two compounds: prostaglandin synthase and lipoxygenase enzymes.[22] A study reported that 5-ASA induced overall improvement both physically and biochemically against the toxic damage caused by ACR.[24]

Though many studies have found that acrylamide induces testicular toxicity in rats, there is a lack of data suggesting that the use of antioxidant compounds would effectively confer a protective effect against such toxicity. Hence, the aim of our study was to evaluate the testicular toxicity of ACR and compare the antioxidant effects of both vitamin-E and 5-ASA on ACR-induced testicular toxicity.

Materials and Methods

General materials

Plus one acrylamide (PAGE) grade with purity >99.95 was purchased from Pharmacia Biotech (Uppsala, Sweden), 5-ASA 95%, Vitamin-E (DL-α-tocopherol acetate) and > 98% high performance liquid chromatography (HPLC) were purchased from Sigma–Aldrich (Steinheim-Germany). Testosterone kits were purchased from ALPCO Diagnostics (Windham, USA). Unless otherwise mentioned, all other chemicals and materials of molecular biology grade were