

Hormonal Physiological Changes of Testis Resulting From Exposure to Vinyl Cyanide and the Possible Protective Role of β -cryptoxanthin in Male Rat

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Received:29 March 2021 / Accepted: 15 June 2021 Doi: <u>https://doi.org/10.54172/mjsc.v36i2.58</u>

Abstract: Vinyl cyanide (VCN) is an aliphatic nitrile product which is extensively used in various synthetic chemical industries. VCN is known to exert toxic actions to human beings as well as experimental animals. The present study was designed to examine the ability of β -cryptoxanthin, a naturally occurring antioxidant, to attenuate VCN-induced testicular toxicity in adult albino rats. Daily oral administration of VCN at a dose level of 30 mg/kg b.w. (7.2mg/ animal) to male rats for a period of 5 days significantly reduced the levels of serum testosterone (T), androsterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) which indicates injury to the testis function. Compared to VCN-treated animals, pretreatment with β -cryptoxanthin and its co-administration with VCN once daily at a dose of 40 mg/kg b.w. (9.6mg/ animal) for 30 days induced a remarkable degree of improvement in the levels of endocrine parameters including T, androsterone, FSH and LH. In conclusion, the present results clearly demonstrate the protective role of β -cryptoxanthin against VCN-induced physiological changes in the testis of rats.

Keywords: Vinyl cyanide; β-cryptoxanthin; Hormones; Testes; Rats.

INTRODUCTION

Vinyl cyanide (C_3H_3N , VCN), also known as acrylonitrile, a highly reactive compound having an active vinyle and cyanide groups, which has been widely used in industry for production of plastics, elastomers, and synthetic fibres and as an intermediate in the synthesis of industrial chemicals and pharmaceuticals (Humans, 1979). It is also used in the manufacture of soft prosthesis material (Parker & Braden, 1990), coating membranes for Langerhans islets implants (Kessler et al., 1992) and high permeable dialysis tubing (Ward et al., 1993).

Human exposure to VCN could potentially occur during the manufacturing process, end product usage and transportation. Further, such exposure can also be possible in the general population through cigarette smoke and via contamination of drinking water (Byrd et al., 1990). VCN demonstrated acute toxicity in testes of rats, mice, rabbits and guinea pigs having a high acute toxicity result from inhalation, and a high to extreme acute toxicity result from oral or dermal exposure (Mathieu-Denoncourt et al., 2015; Thier et al., 2000). VCN is teratogenic in laboratory animals (rat and hamster) at high doses when maternal toxicity has been already manifested. VCN has been demonstrated to induce embryotoxic effects in rat (Saillenfait & Sabate, 2000).

VCN-induced embryotoxic and teratogenic effects have also been found in VCN-exposed workers (Wu et al., 1995). According to environmental teratologic epidemiological study in inhabitants living in the surrounding region of an acrylonitrile factory, three congenital abnormalities (pectus excavatum, undescended testis and clubfoot) in 46,326 infants showed significant time-space clusters in the

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study region. There was a decrease in risk of undescended testis with increasing distance from the acrylonitrile factory (Czeizel et al., 1999). Therefore, women not professionally exposed would appear to be at risk of teratogenic effects due to VCN toxicity.

VCN is rapidly absorbed and distributed to all major tissues in animals. Previous studies with 14C have shown that VCN covalently binds to thiol group of proteins (Ahmed et al., 1982) and tissue macromolecules and nucleic acids (Pilon et al., 1988). Therefore, estimation of free radical generation and antioxidant defence has become an important aspect of investigation in mammals. Carotenoids (β -cryptoxanthin or what is known as β-carotene) are naturally occurring antioxidants that play an important role in animal health by inactivating harmful free radicals produced through normal cellular activity and from various stressors. The antioxidant function of these micro-nutrients could at least in part, enhance the immunity by maintaining the functional and structural integrity of important immune cells (Chew, 1995; El-Demerdash et al., 2004).

 β -cryptoxanthin, aside from being a major source of vitamin A (retinol), an essential vitamin for spermatogenesis to proceed, has been reported to be a potent free radical quencher, singlet oxygen scavenger and lipid antioxidant (Burton, 1989; El - Missiry & Shalaby, 2000) focused on the ability of β cryptoxanthin to function as a chain-breaking antioxidant in a lipid environment at physiological oxygen partial pressures that are considered most likely in mammalian cells. Therefore, the aim of the current study was to investigate the efficacy of β -cryptoxanthine on VCN-induced functional and structural alterations related to oxidative stress in the testes of rats.

MATERIALS AND METHODS

Chemicals: Vinyl cyanide (VCN) and β - ed animal groups cryptoxanthin were obtained from Sigma- the last dose of © 2021 The Author(s). This open access article is distributed under a CC BY-NC 4.0 license. *ISSN: online 2617-2186 print 2617-2178*

Aldrich Chemical Company (St. Louis, MO, USA) and given by oral gavage at dose of 30 mg/kg b.w. (Takano et al., 2010) and 40mg/kg b.w. (Sadir et al., 2007), respectively. All other chemicals and solvent used were of highest available commercial grade.

Experimental animals: Fourty male Sprague– Dawely rats, each weighing 240 ± 10 g. The animals were housed in stainless steel cages after grouping in batches of five animals under standard animal house conditions of relative humidity ($55 \pm 5\%$), temperature (25 ± 2 °C) and a 12 hr light/12 hr dark cycle. Rats were allowed free access to standard commercial feed and tap water and were acclimatized to laboratory conditions for a period of one week before the onset of experimentation.

Experimental protocol: Animals were allocated to four groups each of ten rats as follows: Group I: (Control) pre-treated with corn oil (2 ml/kg b.w.) once daily for 25 days and treatment continued with distilled water (2 ml/kg b.w.) once daily for additional 5 days i.e. from day 26 to day 30 of the experimental period of 30 days.

Group II: (VCN group) pre-treated with corn oil (2 ml/kg b.w.) once daily for 25 days and treatment continued with VCN in a dose of 30 mg in 2ml distilled water per kg b.w. (7.2 mg/ animal) once daily for additional 5 days.

Group III: (β -cryptoxanthin group) pre-treated with β -cryptoxanthin in dose of 40 mg in 2 ml corn oil per kg b.w. (9.6mg/ animal) once daily for 25 days and treatment continued with distilled water (2 ml/kg b.w.) for additional 5 days.

Group IV: (β -cryptoxanthin and VCN group) pre-treated with β -cryptoxanthin (40 mg/kg b.w.) for 25 days and treatment continued with VCN (30 mg/kg b.w) for additional 5 days.

At the end of the experimental period, the tested animal groups were sacrificed after 24 h of the last dose of different administrations and CC BY-NC 4.0 license. their blood were collected by carotid bleeding in centrifuge tubes, serum was obtained from the blood after centrifugation at 3000 rpm for 10 min.

Methods of analysis: Determination of luteinizing (LH), testosterone (T) and androsterone hormones in serum were carried out according to the method of (Jaffe & Behrman, 1974) and follicle stimulating hormone (FSH) was measured by radioimunoassay (RIA) using the method of (Rose, 1998).

Statistical analysis: Statistical analyses of the resulted data were done using In-Stat version 2.0 (Graph Pad, ISI, Philadelphia, PA, USA, 1993) computer software. The results were expressed as means (\pm SE). Multiple comparisons were done using one-way ANOVA followed by Tukey-Kramer as a post-ANOVA test. Statistical significance was accepted at P< 0.001,

P<0.01, P<0.05.

RESULTS AND DISCUSSION

Analysis studies: Data listed in Table 1 show that treatment with VCN caused a significant (P<0.001) decrease in the levels of T, androsterone, FSH and LH, respectively as compared to the corresponding control group. Pre-and co-administration of β -cryptoxanthin to VCNchallenged rats significantly improved (P<0.001) the levels of these hormones as compared to VCN-treated group.

From these results it is clear that vinyl cyanide has been demonstrated to induce male reproductive toxicity in laboratory animals (Ahmed et al., 1992; Liu et al., 2004) and also in VCNexposed workers (Xu et al., 2003).

Table:(1). The effect of vinyl cyanide (30 mg/kg b.w	.) and/or β -cryptoxanthin	(40 mg/kg b.w.)	on serum testosterone,
androsterone, FSH and LH of male albino rats.			

Groupe Hormone	Control	VCN	βcryptoxanthin	βcryptoxanthin +VCN
Testosterone ng /ml	7.05 ± 0.04	3.00± 0.03 (- 57.45%) a**	7.63± 0.09 (8.23%) a**b**	4.62± 0.16 (-34.47%) a**b** c**
Androsterone pg/ml	49.41± 0.29	30.41± 0.22 (-38.45%) a**	52.40± 0.27 (6.05%) a**b**	41.61±0.83 (-15.79%) a**b** c**
FSH pg/ml	10.64± 0.12	4.09± 0.26 (-61.65%) a**	12.61±0.16 (18.52%) a**b**	8.32± 0.22 (-21.80%) a**b** c**
LH mIU/ml	8.96± 0.10	4.51±0.06 (-49.67%) a**	9.26± 0.15 (3.35%) b**	7.48±0.12 (-16.52%) a**b**c**

- Data are expressed as means \pm SE (n = 10 in each group).

- Values between parentheses are the difference % of each parameter with respect to control value.

a: Significant change at P < 0.05 with respect to control group.

b: Significant change at P< 0.05 with respect to VCN-group.

c: Significant change at P< 0.05 with respect to β -cryptoxanthin -group.

**Very high significant change exists at P < 0.001.

Whole body autoradiography and toxicokinetic studies showed that the brain is a target organ for VCN toxicity (Ahmed et al., 1982). (McLachlan et al., 2002)reported that endocrine support is essential for normal spermato

genesis and disturbance can lead to altered spermatogenesis in both humans and rodents. Therefore, the decrease in the levels of serum T, androsterone, FSH and LH could be explained in the current study. The present results are in accordance with the study of (Ivănescu et

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al., 1990) who reported that VCN decreases testosterone synthesis and/or secretion in humans. In this study, the observed decrease in the levels of T and androsterone following VCN administration may be attributed to the increase in oxidative stress. This finding is consistent with that of (Diemer et al., 2003; Mathieu-Denoncourt et al., 2015) who showed that H₂O₂ is a potent oxidant that could inhibit steroidogenesis (reduce testosterone synthesis) in Leydig cells. Similarly, (Yang et al., 2005) reported that serum T level and Levdig cell viability were decreased in rats treated with the structurally similar vinyl monomer, Vinyl cyanide (VCA). Their interpretation is that the decreased viability of Leydig cells caused by VCA treatment lowered testestrone level. which in turn, reduced spermatogenesis in the rat testes. Furthermore, the results of (El-Yamany, 2009) showed a significant decline in serum levels of T, FSH, LH and prolacting (PRL) of rats fallowing VCA administration.

The author attributed the decline of T, FSH, LH and PRL levels to the dysfunction of pituitary gland and also demonstrated that VCA affects the testes directly and/or indirectly through its effect on pituitary gland and decreases the secretion of FSH and LH. Also, the present results are in accordance with the study of (Gunnarsson et al., 2003) who found that cadmium caused a decrease in T production through the decrease in LH receptor messenger ribonucleic acid (mRNA) levels as well as cyclic adenosine monophosphate (cAMP) levesl in rats.

To protect spermatogenesis from toxicant exposure, many clinical and experimental trials of antioxidant agents have been attempted. Carotenoids as potential antioxidant are well known as highly efficient scavengers of singlet molecular oxygen (1O2), and other excited species. The present study indicates the beneficial effects of β -cryptoxanthin against vinyl cyanide induced testicular toxicity. β -cryptoxanthin treatment improved the levels of endocrine parameters including T, androsterone, FSH and LH. These results are in agreement with those

obtained by (Livera et al., 2002) who found that in adult rats, retinoids increased basal testosterone secretion in Leydig cell primary cultures. Also, (Hanukoglu, 2006) reported that the antioxidant enzyme activities superoxide dismutase, catalase, and glutathione peroxidase are parallel steroidogenesis and the antioxidant β-cryptoxanthin exerted a protective role on Levdig cell steroidogenesis to produce testosterone: thus it stimulates the development of reproductive organs through the growth of Leydig and Sertoli cells and the promotion of spermatogenesis. Also, (Silva et al., 2001) suggested that pretreatment with another carotenoid, bixin reduced the total number of chromosome aberrations and inhibited the increase in lipid peroxidation induced by cisplatin. Furthermore, (Gupta & Kumar, 2002) elucidated that the effect of oral lycopene, a naturally occurring carotenoid in tomatoes, therapy in men with idiopathic infertility and found improvement in male infertility and especially in sperm characteristics.

A rational mechanism for the protective effects of β -cryptoxanthin could be the potential antioxidant activity. Because β -cryptoxanthin is a lipophilic substance, it exerts its action in hydrophobic environment such as the lipid core of membranes. Thus, it is anticipated that natural β -cryptoxanthin, a chain breaking antioxidants, can contribute to protecting cell membranes from lipid peroxidation (Krinsky, 1998). β cryptoxanthin can function as an effective antioxidant not only against singlet oxygen but also against lipid peroxidation and the highly destructive, hydroxyl radical OH• that is implicated in many diseases such as cancer and heart disease (O'neill & Thurnham, 1998).

CONCLUSION

In conclusion, this study clearly demonstrated the potential antioxidant benefit of β -cryptoxanthin in managing VCN-induced physiological changes in the testes of rats.

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مجلة المختار للعلوم 36 (2): 174-167، 2021

التغيرات الفسيولوجية الهرمونية للخصية الناتجة عن التعرض لسيانيد الفينيل والدور الوقائي المحتمل للبيتاكريبتوزانثين في ذكور الجرذان

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> تاريخ الاستلام: 29 مارس 2021 / تاريخ القبول: 15 يونيو 2021 https://doi.org/10.54172/mjsc.v36i2.58:Doi

المستخلص: سيانيد الفينيل منتج أليفاتي يستخدم على نطاق واسع في مختلف الصناعات الكيميائية الاصطناعية، ومن المعروف أن سيانيد الفينيل له تأثيرات سامة على البشر، وكذلك حيوانات التجارب. وقد صُممت هذه الدراسة لفحص قدرة بيتاكريبتوزانثين، وهو أحد مضادات الأكسدة الطبيعية، على تخفيف التغيرات الهرمونية للخصية التي يسببها سيانيد الفينيل في الجرذان البيضاء البالغة. وقد أجريت هذه الدراسة على أربعين من ذكور الجرذان البيضاء البالغة، تزن 40±10 جراما، تم تقسيمها إلى أربع مجموعات (10 جرذان لكل مجموعة). تمثل المجموعة الأولى (التي أعطيت زيت ذرة، وماء مقطر) المجموعة الضابطة. وأعطيت المجموعة الثانية عن طريق الفم جرعات من مركب سيانيد الفينيل تعادل 30 مجم/ كجم من وزن الجسم، وذلك على مدار الأيام المحموعة الثانية عن طريق الفم جرعات من مركب سيانيد الفينيل تعادل 30 مجم/ كجم من وزن الجسم، وذلك على مدار الأيام محم/كجم من وزن الجسم لمدة 30 يوماً، أما المجموعة الثالثة يومياً عن طريق الفم جرعات من البيتاكربتوزانثين تعادل 40 محم/كجم من وزن الجسم لمدة 30 يوماً، أما المجموعة الرابعة فقد أعطيت البيتاكربتوزانثين وسيانيد الفينيل مثل المجموعتين الأنية، والثالثة، وبالجرعات نفسها. وتم جمع عينات الدم من مجموعات الجرذان بعد أربعة وعشرين ساعة من إعطاء الجرعات مستويات كل من هرمون التستوستيرون، والأدروستيرون، والهرمون المائسة للحويصلات، وهرمون الجسم الأصفر في مصل الأليم مستويات كل من هرمون التستوستيرون، والأدروستيرون، والهرمون المائسة للحويصلات، وهرمون الجسم الأصفر في مصل الدم مستويات كل من هرمون التستوستيرون، والأدروستيرون، والهرمون المائسة للحويصلات، وهرمون الجسم الأصفر في مصل الدم مستويات كل من هرمون التستوستيرون، والأدروستيرون، والهرمون المائسة للحويصلات، وهرمون الجسم الأصفر في مصل الدم مستويات كل من هرمون التستوستيرون، والأدروستيرون، والهرمون المائسية للحوسائية، أما المجموعة الرابية المي مستويات كل من هرمون التستوستيرون، والأدروستيرون، والهرمون المائسة للحويصلات، وهرمون الجسم الأمير وينائية في معانين من يومون التستوستيرون، والأدروستيرون، والهرمون المنشط للحويصلات، وهرمون الجسم الأصفر في مصل الدم، معاني التئير قبل وفي وقت متزامن مع سيانيد الفينيل فقد حدث تحسن ذي دلالة إحصائية في مستوي هذه المياي، النيت النيئ البيتائجة قد أوضحت أن للبيتكريترانثين دور وقائ

الكلمات المفتاحية: سيانيد الفينيل، بيتاكربتوزانثين، هرمونات، خصبي، جرذان.

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