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Can vitamins C and E restore the androgen level and hypersensitivity of the vas deferens in hyperglycemic rats?

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Abstract:
Diabetic neuropathy can affect the male reproductive system. The aim of this study was therefore to evaluate whether antioxidant (vitamins C and/or E) treatment could attenuate reproductive dysfunctions in hyperglycemic adult male rats. The animals were randomly assigned to one of four experimental groups: hyperglycemic control (Hy), hyperglycemic + 150 mg/day vitamin C (HyC), hyperglycemic + 100 mg/day vitamin E (HyE) or hyperglycemic + vitamins C and E (HyCE). The normoglycemic group (n = 10) received only the vehicles. The testosterone level and noradrenergic response of the vas deferens were analyzed. Both vitamins significantly decreased the TBARS (thiobarbituric acid reactive species) level in the hyperglycemic groups. There was a significant reduction in the testosterone level in the Hy and HyE groups when compared to the normoglycemic group. However, the testosterone levels were partially recovered in the HyC and HyCE groups. In addition, an increased sensitivity of the α-1 adrenoceptor in the vas deferens of the hyperglycemic control group was observed. Treatment with vitamins partially restored (vitamin E or in combination with vitamin C) or totally (vitamin C alone) this dysfunction. Moreover, the maximum response values to norepinephrine were similar among all groups. Thus, we concluded that vitamin C is more efficient than vitamin E in attenuating the effects of hyperglycemia on the male reproductive system of adult rats.

Key words:
vitamin C, vitamin E, hyperglycemia, testosterone, vas deferens, norepinephrine, male reproductive system, male rat

Introduction

Diabetes, obesity, genetic predisposition and aging are some factors that may lead to a hyperglycemic state. The effects of hyperglycemia may occur through different mechanisms and impact many bodily functions, including reproduction. Sexual dysfunctions, such as decreases in fertility, testosterone levels and sperm count, have been extensively de-

scribed in hyperglycemic males [3, 36, 40, 46]. Autonomic nervous system neuropathy, also known as diabetic neuropathy, has also been described [22, 29, 30, 41, 45] and can damage the ejaculatory process [16, 33, 36, 39]. These neuropathies affect 50–60% of diabetic patients, making them the most common complication in diabetes [9, 19].

Ejaculation is a complex process stimulated by a series of biochemical events and depends on serotonin, dopamine, oxytocin, GABA, adrenaline, acetylcholine [12], testosterone, neuropeptide Y, vasoactive intestinal peptide and nitric oxide, and it is controlled by the sympathetic autonomic nervous system [13, 35]. The central ejaculatory neural circuit comprises the spinal cord and cerebral areas, which form a highly interconnected network. The sympathetic and parasympathetic systems, as well as the somatic spinal centers, under the influence of sensory genital and cerebral stimuli integrated and processed at the spinal cord level, act in synergy to control physiological events occurring during ejaculation [13]. The efferent reflex of the nervous system, responsible for the emission phase of ejaculation, consists of sympathetic efferent fibers of the hypogastric nerve that primarily release noradrenaline, causing propulsive contractions of the epididymis, vas deferens, prostate and seminal vesicle and thus expelling sperm to the prostatic urethra [35]. Many animal studies on the function, biochemistry and sensitivity of α receptors to adrenergic agonists of the vas deferens have shown that the organ machinery is impaired in the hyperglycemic model [22, 28, 29], which can be correlated with ejaculatory dysfunction. Such changes may be related to decreases in testosterone and/or insulin levels [22–24, 28].

Another common consequence of the hyperglycemic state is increased oxidative stress [5, 6, 18, 26, 27], which is extremely toxic to cells and exerts its devastating effects directly, by damaging cellular proteins, lipids, and DNA, or indirectly, by affecting normal cellular signaling and gene regulation [34, 44]. This oxidative stress has a positive relationship with functional, structural and biochemical abnormalities in the autonomic nervous system [9, 15, 19, 34]. To investigate this aspect of hyperglycemia, different types of antioxidants have been utilized to reduce nerve function deficit in experimental conditions and at least partially diminish the complications caused by this disease [34, 44].

Vitamin E (α-tocopherol), a lipid-soluble vitamin, is present in biological membranes and is one of the major biological antioxidants [42]. Vitamin C (ascorbic acid) is a water-soluble vitamin required for multiple biological functions in humans and animals, such as the biosynthesis of collagen, conversion of dopamine to norepinephrine, recycling of α-tocopherol, antioxidant potential [21] and low levels of vitamin C occur in several pathologies [20]. In addition, vitamins C and E have a potential therapeutic role in chronic disease treatment.

In spite of the information above, almost nothing is known about the possible protective effect of vitamins C and E on the isometric contractions of the vas deferens in streptozotocin- induced hyperglycemic rats. This effect may be related to male reproductive system dysfunctions that alter ejaculation and sperm transit through the epididymis. Günes et al. [15] have shown that the use of antioxidants (stobadine and vitamin E) in hyperglycemic rats might be an effective therapy for restoring sympathetic neurotransmission in the vas deferens.

Based on these facts and on the clinical relevance of this subject, as well as on the lack of information in the scientific literature, this study aimed to verify whether treatment with vitamin C and E (alone or in combination) was able to attenuate or eliminate the effects of hyperglycemia on the male reproductive system of adult rats.

Materials and Methods

Animals

Adult male Wistar rats (90 days old; 350–410 g) were supplied by the Multidisciplinary Center for Biological Investigation, State University of Campinas (CEMIB – UNICAMP) and were housed in polypropylene cages with laboratory-grade pine shavings as bedding. Rats were maintained under controlled temperature (23 ± 1°C) and lighting conditions (12 h light/dark photoperiod, lights switched off at 7:00 a.m.). Rat chow and filtered tap water were provided *ad libitum*. The experimental protocol followed the Ethical Principles in Animal Research of the Brazilian College of Animal Experimentation and was approved by the Biosciences Institute Ethics Committee for Animal Experimentation (022/06-CEEA) – UNESP Botucatu.