



Endocrine pharmacology

Dietary protocatechuic acid abrogates male reproductive dysfunction in streptozotocin-induced diabetic rats *via* suppression of oxidative damage, inflammation and caspase-3 activity

Isaac A. Adedara^a, Edozie S. Okpara^a, Esther O. Busari^a, Olubunmi Omole^a, Solomon E. Owumi^b, Ebenezer O. Farombi^{a,*}

^a Drug Metabolism and Toxicology Research Laboratories, Department of Biochemistry, College of Medicine, University of Ibadan, Ibadan, Nigeria

^b Cancer Research and Molecular Biology Unit, Department of Biochemistry, College of Medicine, University of Ibadan, Ibadan, Nigeria

ARTICLE INFO

Keywords:

Diabetes
Reproductive dysfunction
Protocatechuic acid
Antioxidant
Inflammation

ABSTRACT

Clinical and experimental studies demonstrated that reproductive dysfunction is a non-lethal complication of diabetes. Protocatechuic acid (PCA) reportedly elicited several pharmacological effects in diabetic animals. However, there is paucity of information on the role of PCA in reproductive dysfunction associated with diabetes. The present study investigated the influence of PCA on the functional changes along the hypothalamic-pituitary-testicular axis in male diabetic rats. Streptozotocin (STZ)-induced diabetic rats were orally treated with PCA at 25 and 50 mg/kg body weight for 45 consecutive days. Results showed that PCA treatment significantly dwindled blood glucose level as well as prevented diabetes mediated decrease in body weight gain and organosomatic indices of the testes and epididymis in the treated rats. Moreover, PCA increased the reproductive hormone levels, marker enzymes of testicular function and sperm functional characteristics in the treated rats. Further, PCA augmented the antioxidant status, inhibited lipid peroxidation and suppressed pro-inflammatory biomarkers including myeloperoxidase (MPO) activity, nitric oxide (NO) and tumor necrosis factor alpha (TNF- α) levels as well as caspase-3 activity in hypothalamus, testes and epididymis of diabetic rats. Collectively, PCA effectively abrogated reproductive deficits in diabetic rats *via* mechanisms involving suppression of oxidative stress, inflammation and caspase-3 activity along with enhancement of sperm functional parameters. Thus, PCA may preserve reproductive health in humans suffering from diabetes.

1. Introduction

Diabetes mellitus is an endocrine and metabolic disorder characterized by chronic elevated blood glucose level due to defectiveness in insulin secretion or action or both. It is a current global health concern because over 400 million people worldwide are affected and it is predicted to increase to over 600 million in 2040 (IDF, 2015; WHO, 2016). Clinical and experimental data demonstrate that diabetes adversely impact reproductive function especially males at the acme of their reproductive years which consequently contributes to the general decline in male fertility rates (Jelodar et al., 2010; Maresch et al., 2018). Infertility is well-known to be a non-lethal complication in diabetic patients (WHO, 2006; Alves et al., 2013). The male reproductive system consists of three components namely the pre-testicular (neuroendocrine regulation), the testicular (spermatogenesis) and the post-testicular (ejaculation) components (Sexton and Jarow, 1997).

Indeed, previous studies demonstrated that diabetes affected the hypothalamus–pituitary–gonadal axis (Kim and Moley, 2008; Schoeller et al., 2012) as well as erectile and ejaculatory function (Kizilay et al., 2017).

Several mechanisms including induction of oxidative stress, inflammation and apoptosis have been reported to participate in the development of infertility in diabetic men (Amaral et al., 2008; Condorelli et al., 2013). Oxidative stress has been implicated as a major cause of male infertility in diabetic animals (Heeba and Hamza, 2015; Adedara et al., 2015). Hyperglycemia is well-known to be associated with active redox cellular functions which consequently results in excessive generation of reactive oxygen species (ROS), tissue injury and inflammation (Amaral et al., 2008; Condorelli et al., 2013; Roessner et al., 2012). Thus, the development of efficient strategies to prevent or delay the occurrence of diabetes and its associated complications is critical. The effective and safe approaches to glycemic control, which is central to

* Corresponding author.

E-mail address: olatunde_farombi@yahoo.com (E.O. Farombi).

<https://doi.org/10.1016/j.ejphar.2019.01.033>

Received 29 November 2018; Received in revised form 15 January 2019; Accepted 18 January 2019

Available online 26 January 2019

0014-2999/ © 2019 Published by Elsevier B.V.