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ORIGINAL ARTICLE

Spermatotoxic effects of galactose and possible mechanisms of action

Toyin Muhammed Salman [a], **Luqman Aribidesi Olayaki** [a], **Isiaka Abdullateef Alagbonsi** [a,b,*], **Adeoye Oyetunji Oyewopo** [c]

[a] *Department of Physiology, College of Health Sciences, University of Ilorin, Ilorin, Kwara, Nigeria*
[b] *National Health Insurance Scheme, North Central A Zonal Office, Kwara State Ministry of Health Premises, Ilorin, Kwara, Nigeria*
[c] *Department of Anatomy, College of Health Sciences, University of Ilorin, Ilorin, Kwara, Nigeria*

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Abstract While numerous studies have documented the ovotoxic effect of galactose, few available studies on male gonad are of the opinion that it seems to fully escape the toxic effects galactose exerts on the ovary. The present study was therefore designed to further investigate the effects of galactose on male sperm parameters and some reproductive hormones. Thirty male albino rats (200–250 g) were randomly divided in a blinded fashion into 6 groups ($n = 5$). Group A received normal saline and served as control. Groups B, C, D, E and F received 3 mg/kg, 10 mg/kg, 20 mg/kg, 30 mg/kg, and 40 mg/kg of galactose respectively through oral gavage for 42 days. The results showed that chronic administration of galactose promotes sperm toxicity by reducing epididymal sperm count, motility and percentage of morphologically normal sperm. Moreover, galactose increased luteinizing hormone but slightly decreased testosterone and had no effect on follicle stimulating hormone. Galactose also caused a slight decrease in superoxide dismutase and increase in lactate dehydrogenase activity but no effect on catalase. The present study thus showed that chronic administration of galactose could promote sperm toxicity which could be mediated partly by oxidative stress. Moreover, the response of the hormones is similar to that in premature ovarian insufficiency (POI) in female galactosemic model.

1. Introduction

Glucose and fructose are two of the most commonly found monosaccharides in mammalian seminal plasma, although other sugars, such as sorbitol or mannose, can also be detected (1). The presence of either glucose or fructose can affect the function of mammalian spermatozoa in several ways. Glucose concentrations of about 5 mmol l^{-1} produce much higher

* Corresponding author at: Department of Physiology, College of Health Sciences, University of Ilorin, Ilorin, Kwara, Nigeria. Tel.: +234 8067509458.
E-mail address: easylat@gmail.com (I.A. Alagbonsi).
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penetration rates than do fructose or mannose in human spermatozoa (2). Moreover, glucose, but not fructose, produces a high fertility rate and capacitation-like changes in the chlortetracycline fluorescence pattern of mouse spermatozoa subjected to 'in vitro' capacitation (3).

The beneficial (4–8) and detrimental effects (9,10) of glycolysable sugars in male fertility have been well reported. Supplementation of glucose in drinking water improved semen qualities, plasma total protein, cholesterol, and globulin; but decreased abnormal and dead sperm in rabbit (11). It also improved ejaculate volume in broiler breeders (12) and sperm motility in dog (13). Previous reports on the effect of glucose on plasma testosterone are controversial. For instance, increase in testosterone level in rabbit (11) and decrease in human (14) following oral glucose ingestion have been reported. However, Attia et al. (12) and Hotzel et al. (15) reported no effect in broiler breeders and Merino rams respectively. Decrease in luteinizing hormone following oral glucose ingestion has also been reported (14).

Galactose is a monosaccharide similar to glucose and fructose but the three sugars have different stereochemistry. The impairment of ovarian function in classical galactosemia has been known for over 35 years (16). Galactosemia, an inherited inborn error of the major galactose assimilation pathway caused by galactose-1-phosphate uridyltransferase (GALT) deficiency, produces wide phenotypes of ovarian dysfunction (17). The prevalence of premature ovarian insufficiency (POI) in galactosemic population is 1 in 10,000 for women between 15 and 29 years of age, and 7.6 in 10,000 for women aging between 30 and 39 (18). In some women, ovarian failure is a consequence of premature depletion of follicular reserve (afollicular or follicle depletion type of POI), while the other galactosemic women do exhibit the presence of follicles that are refractory to gonadotropin stimulation and therefore suffer from arrested growth and maturation (follicle dysfunction type of POI or resistant ovary syndrome) (19). Despite more than four decades of intense research, the cause and effect relationships between galactosemia and POI, and the molecular mechanisms of galactose toxicity remain elusive; however, the general consensus is that the ovarian pathology is the aftermath of toxic effects of galactose and its metabolites both at the ovarian and extra-ovarian levels (20–22).

Previous studies have used rats placed on high dose of galactose as a model for galactose toxicity. For instance, experimental galactose toxicity in female rats produced an array of ovarian dysfunctions that characterize the basic tenets of diverse phenotypes of POI (23). Moreover, embryos exposed to high galactose *in utero* suffer from significant attenuation of germ cell migration and develop ovaries with deficient follicular reserve (24). Liu et al. (25) reported that high galactose diet down regulated the oocyte specific growth factor, GDF-9, an obligatory factor for folliculogenesis, leading to inhibition of follicular development. Lai et al. (26) have also reported an apoptotic effect of high galactose diet on the ovary.

However, despite all the documented findings on the toxic effect of galactose on ovary, there seem not to be any published reports on a possible impairment of the reproductive outcome in human galactosemic males, nor is there any gonadal toxicity in male offspring of galactose-fed rats (27). Forges et al. (17) concluded that the male gonad seems to fully escape the toxic effects galactose exerts on the ovary. This has been underlined since the initial descriptions of ovarian failure in galactosemic patients: in eight male galactosemics aged between 13 and 28 years, pubertal development occurred normally, and serum gonadotropin and testosterone levels were in the normal range for all patients (28). Normal testosterone levels were also detected by other authors in 10 galactosemic males; however, in the three oldest (21–24 years) of them, elevated serum FSH was measured (29).

A recent study by Yu et al. (30) changed the impression that the male gonad seems to fully escape the toxic effects galactose exerts on the ovary. For instance, the authors reported that galactose administration caused down-regulation of sperm motility, which was regained with diosgenin (a material for the synthesis of dehydroepiandrosterone which is a precursor of testosterone) treatment. However, testosterone production was not affected by galactose treatment but was decreased in diosgenin rats exposed to galactose. They concluded that the down-regulation of reproductive function in galactose-induced aging model of rat is via reduction in sperm motility but not via testosterone production.

However, the study of Yu et al. (30) was not comprehensive enough to erase previous long-standing belief that the male gonad seems to fully escape the toxic effects that galactose exerts on the ovary as the parameters measured (sperm motility and testosterone) were not sufficient to do so. For instance, other characteristics of sperm such as count, morphology and viability all of which will help to ascertain whether or not normal spermatogenesis takes place in galactose-treated rats were not investigated by Yu et al. (30). Moreover, the study did not provide any information on the mechanism of galactose-induced sperm toxicity. Hence, there is a need for further information on the spermatotoxic effect of galactose in male rats, which this study aimed to provide.

2. Materials and methods

2.1. Animals and treatment protocol

Thirty male albino rats (200–250 g) were obtained from the Animal House of the Department of Biochemistry, Faculty of Life Sciences, University of Ilorin, Kwara State, Nigeria. They were housed at room temperature and allowed free access to food and water *ad libitum*. "Principles of laboratory Animal care (NIH publication No. 85-23, revised 1985)" were followed. All experiments have been examined and approved by our institutional ethics Committee.

After 2 weeks of acclimatization to their new environment, 30 animals were randomly divided in a blinded fashion into 6 groups (5 rats per group) that received treatment as described below:

(A) Treated with normal saline for 42 days through oral gavage and served as control.
(B) Treated with 3 mg/kg of galactose through oral gavage for 42 days.
(C) Treated with 10 mg/kg of galactose through oral gavage for 42 days.
(D) Treated with 20 mg/kg of galactose through oral gavage for 42 days.
(E) Treated with 30 mg/kg of galactose through oral gavage for 42 days.
(F) Treated with 40 mg/kg of galactose through oral gavage for 4 days.