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Aspirin affect on reproduction of male rat an-overview

Abstract

Aspirin (Acetylsalicylic acid) is used widely in human and veterinary as cardiovascular prophylaxis and as anti-inflammatory, anti-clotting agent and to decrease cancer risk. But there is a deficiency of information about its effects on androgenic studies histology of the testes, kidneys and livers and reproductions. In this paper we tried to collect the information about it deleterious toxicity effect on male rat reproduction and the reason of its side effects. Our finding shows that Aspirin has deadly effect the production of sperm, decrease the testis weight, decrease the production of testosterone and also affect the blood profile. Effect of aspirin on the male reproductive system may be due to being a Prostaglandins inhibitor, and According to all our findings probably it indicates that aspirin have deleterious effect on reproduction and the blood chemistry of male rats

Keywords: aspirin, toxicity, male rat, spermatogenesis, haematology

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Introduction

Aspirin (Acetylsalicylic acid) was introduced to treating human more than 100years ago[1] due to its anti-inflammatory and anti-pyretic benefits it is widely used in clinical settings. First of all it was reported by Vane JR[2] that aspirin and non-steroidal anti-inflammatory drugs inhibit the synthesis of pro-inflammatory prostaglandin E2.lattor on it was reported that aspirin has inhibitory effect on cyclooxygenase-1 (COX-1) activity by acetylating serine 530[3] and COX-2.[4]

Aspirin has been reported effected response to decrease the risk of cancer,[5] Heart problems[6] due to its anti thombotic action.[7] The anti-platelet effect of aspirin has been tested in various forms of coronary artery disease, pregnancy-induced hypertension and preeclampsia in angiotensin-sensitive primigravida at low dosage and showed positive results in most of the reports.[8] Today aspirin is most widely used medicine all over world, according to estimation 4000tonnes of it is used every year.[9]

On other hand it is also reported that it has many adverse effects like long term use of it causes gastro intestinal,[10] stomach problem, and cerebral problems.[11] The increase in incidences of infertility in male due to frequent use of a number of therapeutic drugs has made efforts to study their untoward side effects on the male reproduction. Various drugs used for treating diseases are reported to cause male infertility approximately 50% of infertility is related to problems in male.[12] One of very worse effect of aspirin is on reproduction of male. It was reported that aspirin caused a significant decrease in the weight of testis of immature rats.[13] Decrease in the activities of sorbitol dehydrogenase and hyaluronidase.[14] Decrease in the number of spermatids and increase in size of spermatocytes nuclei were observed.[15] The process of spermatogenesis and the accessory reproductive organs function are dependent on androgen activity. Aspirin administration to normal rats resulted in hypercholesterolemia that's might be due to decreased androgen production, which resulted in accumulation of cholesterol in testes.[13] The impaired sperm dynamics, including spermatogenesis, could be an outcome of aspirin-induced alteration in cholesterol metabolism in testis.[16]

Effect on weight of testis

It was reported that during development around the 33rd day there is an abrupt increase in testicular weight in male rats.[17] Other secondary sexual characteristics mature between 41 and 54days and males reach adult body weight after 54days of age.[18]

The Seminiferous tubules and contents are the primary contributor to testicular weight. The process of spermatogenesis occurs in the Seminiferous tubules of the testis and within the Seminiferous tubules testosterone is the major androgen present.[19] Either a decreased length of Seminiferous tubules or a decreased density of elements within a given length including decreased density due to degeneration of spermatogenic elements would affect testes weight and decreased length of Seminiferous tubules implies either fewer spermatogonial stem cells or a lower mitotic activity of these stem cells.[20] Testis weight are correlated with fertility because larger testicular weight have been associated with an increase in daily sperm production, daily sperm output, Sertoli cell numbers and smaller testis is associated with poorer fertility due to less no of sperm production.[21]

Aspirin decrease the testicular weight,[13] decrease in the weight and nuclear volume of the Leydig cells indicates that Aspirin alters the steroidogenic function of the Leydig cells.

On other hand aspirin did not have any effect on body weight which is sign that aspirin was not toxic to the animals as well as non-androgenic in nature, since androgens are known to posses anabolic activities like stimulating the development and growth of the skeleton and skeletal muscles.[22]

Effect on sperm dynamic

In a germ cell's path to make a spermatozoon from a spermatogonium, a spermatogonium divides by mitosis in the basal compartment, of the seminiferous tubule, to produce either stem cells or committed spermatogonia that ultimately become primary spermatocytes. These cells pass through the blood-testis barrier of the Sertoli cell tight junctions as they move into the adluminal

compartment. They continue their development in the immunologic-protected site of the adluminal compartment.[23] Hyper activation of sperm is essential prerequisite for penetration through the cumulus mass and zona pellucid.[24] A variety of agents in mild to moderate concentrations are known to inhibit sperm hyper activation in vitro including amino acids neurb transmitters calcium channel blockers, calmodulin antagonists and analgesics.[25]

Sperm maturation within the epididymis of the rat has been shown by the greater ability of spermatozoa collected from the cauda epididymidis, over those from the caput, to fertilize eggs after insemination into the uterus.26 But according to founding rat treated with aspirin had decreased no of sperm.[13]

The effects of aspirin in the total number, motility, and effectiveness of the sperm are the most important factors affecting fertility, Increase the number of dead sperm to half of the total leads to complete infertility.[14] The ability of aspirin to affect the motility is the sign that aspirin was able to permeate the blood-testis barrier with a resultant alteration in the microenvironment of the inner part of the wall of the Seminiferous tubules.[22] Aspirin not only decreases the no of sperm and its motility but also including to it causes the decreased in increase in percentage of morphological abnormal sperm cell that may be due to interference of aspirin in spermatogenesis process or due to interaction of testosterone on hypothalamic release factor which can cause changes in spermatogenesis.[27] Aspirin can uncouple oxidative phosphorylation in addition to its COX inhibiting activity,[28] this pathway of action can also contribute for the aspirin induced impairment of sperm hyper activation.

Gholami M et al.[29] explained that giving aspirin to adult mice cause a decrease in the activity of certain enzymes such as Hyalurounidase, which is secreted by sperm and contributes to the process of ovarian Penetrate rubble during the process of fertilization. The effect of aspirin can be through the impact on the flow of calcium into sperm which is necessary for the formation, activation, and movement of sperm.[30]

Aspirin-induced reduction in sperm dynamics might be an outcome of depressed levels of androgens. Interestingly, subchronic aspirin administration influenced androgen dependent parameters including that of reduced sperm count, motility, and density. The observed reduced sperm activity profile might be an outcome of androgen depletion at target level, particularly in the cauda epididymis, thereby affecting physiological maturation of the sperm.[13] Decrease in activity of hyaluronidase, decrease in number of spermatid and increase in size of spermatocytes nuclei is the sign that aspirin cause impairment on later stage of spermatogenesis.

Effect on hormones production

Testosterone is the principle male sex hormones in mammals, birds and other vertebrates; it is produced in the leydig cells within the testes.[31] Primary action of testosterone is anabolic growth, spermatogenesis promotion and promotion of secretion from the accessory sex glands. Testosterone plays an important role in increasing the Fertilization portability of sperm *in vivo* and *in vitro*.[32] Testosterone receptor (androgen receptor) are present on Leydig cells, peritubular cells and Sertoli cells but in germ cells of the mature testis have no any receptor[33] that's why testosterone don't target germ cell directly, instated of that testosterone target the sertoli cell and these sertoli cell nourish the germ cell to differentiate in spermatozoa.[34] Testosterone is the maintenance and reforming of the blood-testis barrier that blood–testis barrier provides a specialized environment for the development of the germ cells and prevents immunogenic germ cell antigens from reaching the immune system.[35] Aspirin treated group is possibly an indication of testosterone deficiency.[36] Aspirin treatment causes a decrease in Leydig cell function, change in Sertoli cell morphology,[37] so it can cause decrease in testosterone production.[22] Testosterone levels in the adult testis of rat should be likely stable and high because germ cell development does not progress beyond the pachytene stage of meiosis if its level is unstable or low.[38] It was found that aspirin has anti androgenic effect; alter masculinisation and potent inhibitors of prostaglandin (PG).[39]

When LH binds to the Leydig cells, it stimulates the cellular messenger cAMP to activate protein kinase A. Protein kinase A undergoes a series of phosphorylations that in turn activate a series of enzymes that synthesis testosterone from the cholesterol base molecule.[40] Aspirin decrease the production of luteinizing hormones which lead to decrease in decrease testosterone hormone, a significant effect in decrease the effectiveness of sperm, as that testosterone hormone increases the secretions of the epididymis and seminiferous tubules which has an important role in transmission of sperm.[14] Including to it testosterone is also required to release of sperm, In the absence of testosterone, mature sperm are phagocytized by the Sertoli cells.[41]

Histological effect on testes

Testis is composed of seminiferous tubules and interstitial tissues. Seminiferous tubules are the site for spermatogenesis and they contain three types of cells: male germ cells, Sertoli cells, and myoid cells, while Leyding cell are locate between neighboring Seminiferous tubules.[42] According to developmental progression at the base of the Seminiferous tubules have Spermatogonia, spermatocytes in the middle, and spermatids near the apex of the Seminiferous epithelium.[23] The aspirin treated rats showed cytological and nuclear degenerative changes in Seminiferous leading to shrinkage to Seminiferous tubules.[13]

In Seminiferous tubules Sertoli cells are the most important cell as because germ cell proliferation depend on it, it provides the nutrition to growing germ cell including to it Sertoli cells are involved in the release of spermatids into the Seminiferous tubule lumen[43] blood test is barrier, regulating the testicular vasculature.[44] leyding cell are involve in production of reproductive hormones.[19] It was reported that aspirin toxicity caused the reduction primary spermatogonia, secondary spermatogonia, spermatocytes, and Leydig's cell.[13]

Ablating Sertoli cells germ cells, seminiferous tubules leyding cell results in reduction in testis size. The impairment of spermatogenesis partly originates from abnormal quantitative increment or functional maturation of Sertoli cells.[45] Decreasing in number of Sertoli cell result decreased intratesticular vascular volume, decrease in number of germ cell, increased permeability of the blood-testis barrier, and structural changes in the Leydig cells and decreased testosterone secretion.[46] Decreased testicular vasculature leads to a reduction in fluid exchange between the vasculature and testicular interstitial, which reduces gonadotropins-stimulated circulating testosterone concentrations, indicative of reduced Leydig cell stimulation and/or reduced secretion of testosterone into the vasculature leading to infertility.[44]

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Effect on blood profile

Blood is a complex two-phase fluid, made up of plasma and formed elements. The formed elements consist of RBCs or erythrocytes, white blood cells (WBCs or leukocytes) and platelets.

The primary function of RBCs is the transportation and delivery of oxygen to the peripheral tissues. However, their mechanical and flow properties are responsible for the complex fluid dynamics which occur in micro vessels.[47] As a corollary, altered biomechanical properties of RBCs can result in impaired oxygen and nutrient supply to peripheral tissues.[48] According to finding of[14] low doses aspirin don't have any significant effect on production of RBCs, but on other hand it significantly reduces the production of Leukocytes.[13] Leukocytes in addition to their primary role in inflammation and immune system also play a part in modulating blood flow.[49] So suggests that decrease in number of WBC the compromised immune system and significant reduction in monocyte count probably indicates that the phagocytic function of the body has been compromised by aspirin.[50]

Aspirin causes significant reductions in packed cell volume (PCV) and haemoglobin(Hb) values[13] and it induction of anaemia and decrease in oxygen- carrying capacity of the blood as well as the amount of oxygen delivered to the tissues.[51] Including to all this it is also reported that sub-chronic aspirin treatment in both low-dose and in low-followed-by-higher dose significantly potentiated the glucose lowering effect of.[52]

Conclusion

Aspirin is worldwide extensively used medicine both in human and veterinary side. But Aspirin toxicity has deleterious effect on the blood chemistry and reproductive efficiency of Male. So, it is recommended that caution should be exercised in the use of aspirin.

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Conflict of interest

Author declares that there is no conflict of interest.

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