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Hormonal effect on male fertility and stem cell survival

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Abstract
Hormonal protection through suppression was proven excellent for the stem cell survival in testis, where as in other tissues it remains obscure. The protection of male infertility through hormonal suppression was done mainly using testicular Hormones like FSH and testosterone, whereas Growth Hormone is mainly involved in neuroprotective effects and ischaemia compared to male fertility. Substances like resveratrol, also protect male fertility by improving the motility of sperm. Stem cell survival through hormonal suppression and protective effects of other compounds like resveratrol against sperm motility was proven to be useful to the mankind with respect to male infertility.

Keywords: FSH, LH, testosterone, hormonal suppression, stem cells

Introduction
It is necessary to study the causes of male infertility as it constitutes about 50% of the total population infertility cases. The causes for male infertility can be divided in to three types namely pre testicular, testicular and post testicular. Pre testicular male infertility involves problem in secretion of pituitary and hypothalamic Hormones and testicular is due to improper testicular function where as post testicular is due to physical causes like obstruction in secretion of sperm (Marvin L. Meistrich *et al*., 2008) [8]. So, use of hormonal therapy in the treatment of azoospermia is proven to be useful as it causes increase in survival of stem cells and results in restoration of sperm count.

Hormonal protection by suppression and regain of spermatogenesis after treatment in males are proven to be effective against neoplastic damage of testis. Further the study on the mechanism of protection against infertility by Hormones is necessary as the gonadal - pituitary axis (Glode *et al*., 1981) renders testis more resistant to chemotherapy.

Study on male gonadal toxicity caused by antineoplastic agents is mainly due to damage to the somatic environment that maintains stem cells. However the amount of recovery depends on the dosage of chemotherapeutic drugs. If the dosage is found to be high, in that case recovery from damage is prolonged or even permanent also. Survived stem cells restore the sperm count by differentiation and studies on spermatogonial cell kinetics show most of the survival pathways and expression of anti-apoptotic proteins are increased after treatment.

Bcl2 is one of the major antiapoptotic protein that prevent the release of Cyt C from mitochondria and other antiapoptotic proteins include Bcl-XL, Bcl-W (Yoshihide Tsujimoto, 1998) [12] which have the same effect like that of Bcl2. Alkylating agents like cyclophosphamide causes male infertility. There are reports that pre hormonal treatment of growth Hormone before irradiation can give protection against procarbazine (N. PARCHURI *et al*; 1993) [9]. This review focuses mainly on hormonal protection of male fertility, the mechanism and the kinetics of the spermatogonial cells.

Androgens effects on male fertility
Estrogens have both direct and indirect effects on protection of nerve cells and glial cells. Indirect effects include increasing blood flow through the brain and vascular endothelial improvement where as direct effects are antioxidant responses, tissue and humoral immune responses, inhibition of aminoacids activation, ca2+ homeostasis and activation of early immediate genes (Pakulski C *et al*; 2011) [10]. Androgens like testosterone proved to increase protection against spermatogenesis through tubule regeneration in rats when pre treated with it. (Gunapala Shetty *et al*., 2005) [3].

Neuroprotective effects of GH after exposure to radiation
In case of irradiated rats growth Hormone levels found to be increased in contralateral hemispheres whereas the insulin like growth factor-I and IGF-I receptor are up regulated in the left hemisphere. Hypoxia and ischemia induced rats were protected against ischemia through tissue regeneration when treated with GH compared to the intact ones. (Katarina Gustafson *et al*., 1999) [5].

GH protection against hypoxic ischaemia
Growth Hormone protection against hypoxic ischemia is through association with neural antigen NeuN which co localises in the nucleus along with GH. Cell viability was profoundly increased in GH treated rats and expression of GH was found to be high in cerebellum part of the brain associated with normal morphology of neurites. The protection against hypoxic ischaemia was already proved in case of GH treated chick embryonic brain when combined with low glucose treatment compared to treatment with GH alone. (Clara Alba-Betancourt *et al*., 2013) [2].

GH has increased the cell survival up to 1.5 fold compared to low glucose treatment and was also shown to activate Akt signaling pathway, the survival pathway in many cells and increases the levels of Bcl2 protein an antiapoptotic protein supported by decreased levels of caspase enzyme. The chick embryonic brain was shown to contain a 15 KDa protein fragment of GH which protects the chick embryo brain against hypoxic condition. (Clara Alba-Betancourt *et al*., 2013) [2].

Other effects of growth Hormone and resveratrol

GH was known to protect against homocysteine by reducing DNA fragmentation with no change in PARP and Bax levels but has strong immunogenic properties with antibodies against Bcl2 protein (Jin-Young Chung *et al*; 2015) [4]. In addition to above effects GH treated rats showed recovery from low weight and imbalanced motor action compared to untreated ones. (Jin-Young Chung *et al*; 2015) [4].

In addition to GH, resveratrol maintains male fertility by improving the sperm motility in a dose dependent manner (Xiangrong cui *et al*; 2016) [11].

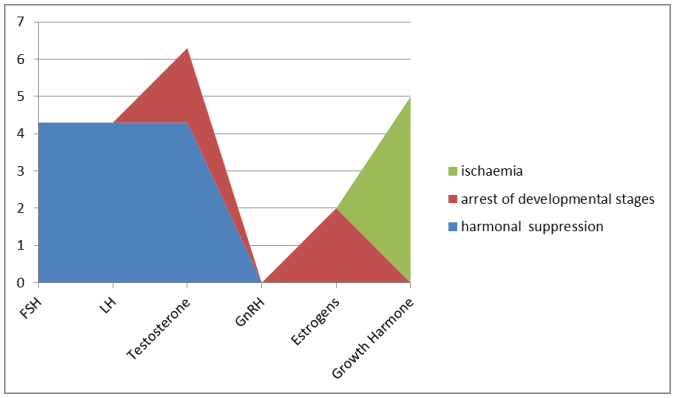

Fig 1: Graph of various Hormones and their protective effects on male infertility. Growth Hormone mostly protects ischaemia where as the estrogens and testosterone causes arrest of developmental stages of spermatocytes and FSH, LH and testosterone are mostly involved in the stem cell survival.

Protection against male infertility through hormonal suppression

Hormonal suppression was one of the techniques used to regain male fertility after irradiation or treatment with anti neoplastic drugs. In baboons protection against cyclophosphamide was observed after treatment with Gonadotropin releasing Hormone (GnRH) agonists whereas Testosterone inhibits the differentiation of spermatogonia in cancer treated patients The hormonal suppression includes blockage of survived stem cells to not to undergo differentiation otherwise which will die after oncogenic insult. Treatment with testosterone agonists decreased the sperm count, but through above mechanism hormonal suppression lead to recovery from the damage and showed normal sperm count through differentiation of survived stem cells in to spermatogonia. Similarly FSH administration before irradiation showed increased cross section in seminiferous tubules containing type A spermatogonia cells. (Aslan Demir *et al*., 2015; Marvin L. Meistrich, *et al*., 2000) [1, 7].

Study on spermatogonial kinetics

Analysis of spermatogonial kinetics by flow cytometry proved that testosterone and estradiol pre treated irradiated rats leads to arrest in division mostly at the stage of late spermatids but not at the spermatocytes. In S-phase cells the 2c ratio was found to be 18% in both control and treated rats where as the 2c peak which corresponds to non germinal cells and G1 phase spermatogonial cells remains unchanged (Marvin L. Meistrich *et al*., 1997) [6]. The cell cycle progression after irradiation showed most of the s-phase cells are sperm cells with 40 cycles of division and G1 phase with pre leptotene spermatocytes (Marvin L. Meistrich *et al*., 1997) [6].

Discussion

Growth hormone protective effects on the male fertility were found to be less focussed compared to other Hormones as it is involved in protection against ischaemia. In addition to anticancer drug treatment, obesity also plays a major role in male fertility through change in Hormone expression. Major Hormones that show changes in expression include testosterone, LH, FSH and prolactin. Testosterone levels are decreased remarkably in the abnormal body weight rats compared to the normal rats. Sperm acrosin activity was also reduced in obese rats compared to normal body weight rats. DNA fragmentation was profoundly increased in underweight, overweight and obese rats (Xiangrong cui *et al*., 2016) [11] due to apoptosis as DNA fragmentation is the one of hallmark associated with apoptosis. Previous studies has showed antiapoptotic activity of many Hormones is due to acting via Bcl2.

So, further studies is required for the correct dosage and the development of protection therapies associated with Hormones. In which Stem cell therapy was also proven to be beneficial.

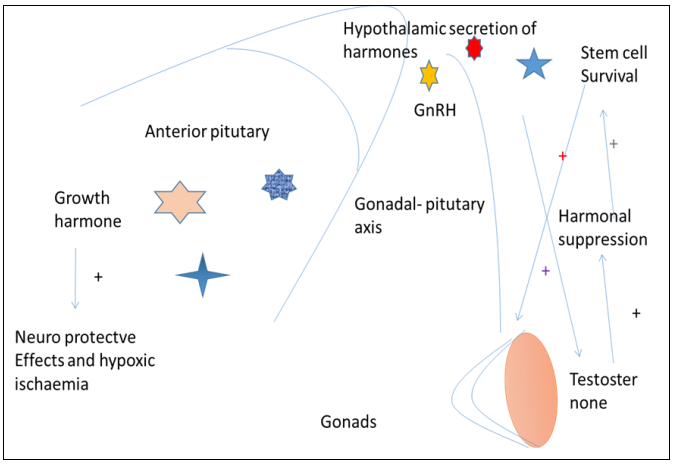

Fig 2: Gonadal -Pituitary axis having protective effects against the male infertility. Growth Hormone show protective effects against neurotoxicity and ischaemia. Where as FSH and LH produced from the anterior pituitary acts on gonads to produce Hormone testosterone from testis and estrogens from the ovary. Testosterone, FSH and LH has been used in the hormonal suppression survival of stem cells which causes reorganisation of gonads.

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Declaration of interest
The author declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported

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