

A Spectacular Visionary of a Human: At the Viral Terrorism on the Messenger Molecules Soldiers, Hormones

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ABSTRACT

Tremendous progress in study of hormones' functions has raised the knowledge about their relationship between normal physiology and disease conditions of the living body. Human cells sensitive to viruses are susceptible to cause an infection. Disease severity is reflected by the number and the nature of cells infected, viral reproduction, inflammation and an immune response of an individuals. Hormones may alter a course of viral infection may be beneficial or detrimental to the host is a study scope as a natural or an experimental challenge for researchers. Hormonal balance is effective to prevent viral infection. Shaping of an immunity is depends on the kinetics of host immune response to virus (initial phase) and an extent of virus induced pathology (T-cell mediated lethality) by the role of HPA (Hypothalamus-Pituitary-Adrenal) Axis, cytokines and glucocorticoids. Hormonal administration after viral infection does not prove to protect the host from disease condition, only supportive to reduce progress and severity of disease status. Efforts by this review is to focus on prevention as a priority rather than curative measures against viruses for human existence.

Keywords: Hormones, Viruses, HPA Axis, Glucocorticoids, Immune –regulating signals.

INTRODUCTION

Hormones are chemical molecular messengers in the human body secreted by an endocrine glands, circulate in the body through the blood and activate target cells (with receptors which correspond to the hormones). About 50 hormones, of nine specialized glands (pituitary, thyroid, four parathyroids, two adrenals and thymus), hypothalamus (nerve center) and number of organs (pancreas, heart, kidney, ovaries, testicles, intestine), control majority of the body functions.¹ Three types of hormones forms are Amides, proteins- peptides and steroids.² Protein type cannot penetrate target cell membrane where steroid type can. HPA axis enlightens the knowledge of an immune–endocrine network. Intestinal Thyroid Stimulating Hormone (TSH) responds by cellular receptors in the viral (REO Virus) infection, determines tissue heterogeneity³.

Viruses are surprise, poorly understood yet pose risk to human health. Due to its antigenic variations,

virus allows faster evolution with mutation even with smaller genome.⁴ From 10¹³ bacteria and 10¹⁴ viruses of gut, about 1200 types of Intestinal commensal viruses, maintain intraepithelial lymphocytes numbers to form firm “great wall” against pathogen invasion to protect the host.⁵ Some enteroviruses benefit the host via immune –regulating signals and design to treat infection, inflammation and cancer.⁵ Any inflammation including to that of lungs is a natural body response to virus through a viral entry into the host via ACE2 receptors on cells. Estrogen and progesterone, are a female sex hormone may reduce ACE2(Angiotensin Converting Enzyme2) receptors by blocking viral entry into cells and reduce fatality rate of females upto 65% compared with that of males.⁶ DNA and RNA of viruses may encode 16 peptide hormones have similar sequence with that of humans. It also encodes similarity of regulatory

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proteins which present in humans.⁷ Hormones of humans and viruses, may explore new insight by this small spectacles. Team efforts of microbiologists, pathologists, druggists and researchers exploring the field of science, is endless for a better survival approach.

DISCUSSION

Hormones vary tremendously in chemical composition, influence on mammalian tissues by multiplicity of its development, growth and functional activities. More than 50 hormones are circulated in the human body, few of them are essential for life. Defects due to deficit or absence of hormones either by infection or by removal of gland are from which they are secreted. Hormonal imbalance causes discordance of activities of other glands or cells / tissues leads to disease state.

Pituitary gland is a pea shaped master gland situated in the brain, regulates vital body functions and controls other hormone secreting glands. It secretes Growth Hormones (GH), Follicle Stimulating Hormones (FSH), Luteinizing Hormones (LH), Adrenocorticotrophic Hormone (ACTH) and many more.¹ Hemorrhagic Fever with Renal Syndrome (HFRS) by HANT Avirus causes edematous hypopituitarism in an acute phase and atrophy and secondary empty sella in chronic phase. Hypotension, hemorrhage, fever, shock, renal failure, ischemia and necrosis are reported due to enlargement of gland.⁸ Hypothalamic –pituitary Insufficiency (HPI) after an Influenza A, herpes simplex and Meningoencephalitis are due to Coxsackie B5 virus is associated with multiple pituitary hormone deficiency. HIV is a cause of pituitary endocrinopathy. Gland infection is increased by toxoplasma gondii and cytomegaloviruses (CMV). Zika RNA virus infection can cause irreversible growth delay and deficit memory in children are due to reduced growth hormones.⁹ Mortality and morbidity by CNS due to History Of Present Illness(HPI) requires focus on early detection and proper treatment plan.¹⁰

Melatonin, a hormone of darkness is secreted by the Pineal gland,¹¹ a pea shaped gland in the brain regulates the sleep-wake cycle. It is also secreted by other organs eg. GI track, bone marrow, including lymphoid cells.¹² It impacts on the mitochondrial metabolism, immune cells and CNS glial cells.

Pharmacological dose of it functions as free radical scavenger¹² and has an antioxidant and immune regulatory role. Exogenous administration of melatonin enhances antibody production. It is used in treatment of sleep disorders, have drawback of initiation of an aging process.¹¹ Dun-Xian Tan, et al.(2014) from the University of Texas had published benefit of melatonin in treatment of epidemic Ebola infections with inflammation, coagulopathy, as well as endothelial disruption like symptoms.^{11,13} Protective effects of melatonin in RSV(Respiratory syncytial virus) infections,¹² a common cause of bronchiolitis in infants of 3years is that it prevents injury to airway structure. It also increases survival of an infant's suffering from septicaemia. Paralysis and death were also prevented in mice by melatonin, which was caused by pathogenic, aggressive Encephalitis Arbovirus (lethal Semliki Forest virus (SFV). This virus is formally related with new corona virus may induce encephalomyocarditis¹²(a lethal inflammation of CNS) as that of in mice. Melatonin use may be a therapeutic alternative to treat VEE (Venezuelan equine encephalomyelitis Virus, arbovirus) and SARS type to rise antibody titre.^{12, 14}

Thymus is a specialized 2 lobed primary lymphoid organ of the immune system located in upper front of chest and heart, behind the sternum. Cell mediated immunity, a part of an immune system which is provided by Thymoxin a tiny protein hormone is secreted by Thymocytes, a T Lymphocytes cells.¹⁵ After pre-adolescent period size of the gland and its activities are decreased and is replaced by fatty changes. Congenital CMV (Cyto Megalo Virus), Hepatitis B and C (HBV& HCV) activate T cells. Persistent or repeated episodes of infections gradually alter thymic structure leads to glandular atrophy.^{15,16} These consequences affect future immune response by impaired functions of pathogen specific T cells. Resistance to infection diminishes with persistence of microbes in HIV patients.¹⁶

Thyroid is a butterfly gland situated in front of the neck below Adam's apple secretes several hormones, amongst them thyroxin hormone is the main regulatory one. Hepatitis C Virus (HCV) causes chronic liver Infection as hepatic and extrahepatic disease manifestations,¹⁷ represents thyroid dysfunction after a period of time. Infectious thyroiditis¹⁸ occurs without viral etiology. Subacute

Granulomatous Thyroiditis (SAT) is characterized as an acute illness with severe neck pain and thyrotoxicosis with typical viral prodromal syndromes, mostly in females. Viral cause is only suspected as viral antibody titres of majority of respiratory and other viruses are ruled out by serological methods in patients of subacute thyroiditis.¹⁹ Unknown and thyroid auto antibodies presence in long duration follow up represent thyroid antigen release response against an inflammation rather than as an autoimmune disease. Inflammation, Autoantibody, aberrant Human Leucocyte Antigen- DR isotype (HLA-DR) and over expression of Toll-Like Receptor(TLR) in an autoimmune thyroid disease ^{17,20} favour virus related pathogenicity in rare thyroid disease types, Hashimoto's thyroiditis(silent thyroiditis),¹⁹ and graves' disease.²⁰ Human T lymphotropic virus-1(HTLV-1)DNA in *Hashimoto's thyroiditis*²⁰and Serum HTLV-I antibody(Human Foamy virus(HFV)) gag proteins in *Graves' disease (GD)* suspect viral pathogen and thyroid disease relationship. Mumps,¹⁹ Influenza and other respiratory viruses (enterovirus) also cause subacute thyroiditis.¹⁸ Along with mumps and enterovirus, rubella, HHV, HCV, HBV, HSV, EBV, CMV, parvovirus are seem to increase risk of thyroiditis anyway.¹⁸

The recent study by Lisa Marie Basile with Leann Poston MD, explored that COVID- 19 caused by SARS-CoV -2 virus causes De Quervain's Granulomatous thyroiditis,²¹a subacute thyroiditis, after infection resolution. 18 days after COVID -19 infection, female patients had neck and thyroid swelling with pain, hoarse voice, difficulty in swallowing, heart palpitation, high inflammatory index (swelling, pain, redness and warmth) with elevated T3 and T4 hormones. DR Poston explained a thyroid hormone secretion is a roller-coaster sort of way. Currently Study by researchers need "deep digging the well" approach to get visionary relation with COVID -19 and dwell with results.²¹ Inflammatory markers, ESR and C-reactive protein are increased in thyroid infection by virus. Steroids and other hormones medications are preferred to treat the disease condition. Amongst HLA-A,-B,-C, Risk of recurrence of SAT as it is HLA dependent, is increased with particular Human Leucocyte Antigens HLA-B*18:01 and -B*35.²²

Adrenal Glands are suprarenal glands, small, triangular located on top of the both kidneys,

regulate metabolism, immune system and body response to stress. Blood pressure regulation is also done through hormone release directly into the blood stream. Nonetheless viruses have clinical or pathological evidence of primary adrenal involvement as an indolent infection cause.²³ Enhanced Th2 (cytokine, a hormonal messenger) response, adrenal deregulation of glucocorticoids occur in progressive HIV.²³ EBV associated adrenal lymphomas and infections are due to HSV in neonates contains higher number of viral particles in the adrenals.²³ Catastrophic adrenal disease with less common haemorrhagic viruses and an Ebola virus lethality was characterized by apoptotic lysis of cells in multiple organs and liquefaction of adrenal glands. Zika virus infections damage the hypothalamus, disturbing an endocrine system leads to retardation of growth and impaired memory in mouse pups and it concerns with infants too.²⁴ Growth hormone has improved growth near normal.²⁵ Peptide invented at Nanyang Technology University by Singaporean Scientists team may be useful to prevent infections.²⁵ Marburg and Lassa virus infect gland with cortical cell damage.²³ SARS CoV and an influenza virus represent an amino acids sequences homology of ACTH to that of humans. Echoviruses and H5N1, a recently affecting Southeast Asia cause a multifocal haemorrhagic adrenal cells necrosis with severe damage to adrenal glands.²³ Central hypoadrenalism and hypothyroidism²⁶ were ruled out in recovered patients of COVID-19 in periodic assessment suggesting transient Hypothalamus-Pituitary-Adrenal (HPA) dysfunction.²⁶ Cortisol dynamics as degeneration and necrosis of the adrenal cortical cells may be altered in an autopsied patients with SARS (and COVID-19 - 2003).²⁷ Adrenal insufficiency leads to infection related deaths in ongoing COVID-19.²⁷ Proinflammatory cytokines activate HPA Axis by release of increase CRH, release ACTH, provoke release of Glucocorticoids in peripheral blood. Glucocorticoids orchestrate fight or flight response (fasten energy supply to critical organs and maintain breathing for rapid transport of nutrients and oxygen) to protect against normal defense reactions (immune response/ inflammation) by turning them off and help maintaining their homeostasis.²⁸ Study of Serum cortisol and ACTH presence in COVID patient need further evaluation to support treatment modality. Lymphopenia with higher level of serum cortisol

data with SARS patients is in report by Panesar et al. guides to survey same in recent COVID -19 patients. Glucocorticoids, as used in other viral infection treatment, (WHO guidance) is under trial in COVID 19 with safe and efficient way.²⁷

Testes and Ovaries are reproductive organs of the males and females produce gametes and sex organs, secrete steroid hormones, a testosterone (male) and estrogen and progesterone (female). Sex steroid hormones, estrogen and testosterone can mitigate an inflammatory response against viral infections. progesterone will also prevent cytokine storms.⁶ Lymphopenia in patients suffering from COVID-19 might doubt about an anti-inflammatory effects of an Estrogen hormones.²⁹ Anticatabolic effect of testosterone on respiratory muscles with its peripheral conversion to estrogen via aromatase enzyme, might add an anti-inflammatory effect and it reduces the need of assisted ventilation in patients infected with SARS-CoV-2.²⁹ Longer intensive care unit stay along with ventilation in patient with acute respiratory infection founds hypogonadism in recent study. SARS-CoV 2 infection may impact on spermatogenesis, needs further larger sample analysis.³⁰ Younger male patients have more protective anti-inflammatory effects against SARS-CoV-2 by testosterone compared with older aged.²⁹ More efficient viral cleaning suggests strong immune functions due to extra X chromosomes in females than that of males. Leydig and Sertoli cells in the testis, oocytes and ovarian tissue have medium –high expression of ACE2 receptor made them vulnerable to damage³¹ Behavioural change of ACE2 expression with age and from early secretory and midsecretory phases in women's menstrual cycle for fertility purpose, have an impact on viral infectivity susceptibility³¹. Chronic hepatitis C infection increases risk of fibroids in menopausal stage in females due to low estradiol level.³² Transmembrane serine protease 2 (TMPRSS2) genes expression on subsequent endometrial phase varies and accompanies with age. These genes supports the viral spike S protein binding on ACE2 receptors through cleaving, have role in change of SARS-CoV-2 infection status and it resets with cycle to cycle and age.³¹ Prolonged period of an infection with COVID-19 may not increase risk of sperm infection and its transmission to embryos during in vitro fertilization due to low

or no expression of ACE2 and TMPRSS2.³³ **Kate E. Stanley** has stated that any viral infection during pregnancy can be fatal to fetus, (eg.H1N1,H5N1) which is defeated by prior vaccination.³⁴ By Elisabeth, a careful approach for ART(antiretroviral therapy) in an older women have reduced the risk of an infections.³¹ Exogenous estrogen and testosterone therapy has value to mitigate damaged inflammatory response to SARS-CoV-2 without impeding immune system's response.²⁹ Acute phase of Mumps Orchitis may affects Leydig's cell functions, lowers the testosterone level and an exaggerates pituitary response on elevated luteinizing hormone-releasing hormone(LHRH). Childhood vaccination programme (2005) has declined incidence of mumps orchitis.³⁵

Parathyroid glands are four small glands located in the neck behind the thyroid from where they monitor and regulate blood calcium level. Gland produces and secretes parathyroid hormones in response to low blood and bone calcium level. Evidence based study suggests no direct viral RNA transcription in an inflammatory thyroiditis due to common tumours of viral etiology³⁶ or known diseases of parathyroids.³⁷

Pancreas is a glandular organ in the upper abdomen, as an exocrine gland, excretes enzymes to breakdown proteins, lipids, carbohydrates and nucleic acids of food. As an endocrine gland it secretes the peptide hormones insulin and glucagon to control blood sugar levels throughout the day. Viral RNA into pancreatic islet cells appears after Human H1N1 and H3N2 virus infections by avian influenza viruses.³⁸ Viral replication in exocrine portion cause fibrosis and disruption of organ architecture by altering B cell architecture. Viremia, Acute pancreatitis and Type 1 Diabetes leads to necrotic damage and impair both functions.³⁸ Type 2 diabetes appears to be higher among patients with HCV- 2.^{39,40,41} Viral hormones, insulin/IGF-1-like peptides (VILPs), show up to 50% homology to human insulin/ IGF-1, are presumed similar 3D structures formation may modify health and disease status in humans⁴² Rapid increase in incidence of Type 1 diabetes observation by many researcher conclude a virus role as an etiology in humans.³⁸ It include Influenza A virus, Enteroviruses, Cocksackievirus B (CVB) Measles virus, Congenital Rubella virus, Mumps virus, Cytomegalovirus, and

Influenza B virus and Rotavirus and Reovirus in mice.

HUMAN: Molecular virologist Thomas Pietschmann and other researchers think that men, women and children are infected with an equal frequency but disease manifestations differ depends on age, gender and previous illness. Immune relevant genes recognise pathogens are encoded on X chromosomes. As women have two X chromosomes, have wider diversity of immune response. It increases general immune response through estrogen hormone but more risk for an autoimmune disease. Children have prenatal innate immunity defence via mother in womb till breast feeding and passive immunization by killer cells till built up their own immunity up to age of 10. Studies till today⁴³ show that hormone testosterone, stressful, irregular lifestyle including habits and difference in chromosomes X and Y, hit the men more by disease susceptibility to infections.

VIRUS: Virus is selfish, naked invisible alien enemy, a nano biological weapon and a lurking danger, full of mysterious fear,⁴⁴ Although it needs an obligation of a live host to be alive. It's a microscopic protein, encoded with few genes which hijacks host cells' DNA, make millions of its own clone inside the cells.⁴⁵ As an earth creature, human has complex relationship with it. Unusual encounter of host cell, explosive spread throughout body, escape via air, water and body fluid and spread as an infectious agent around the globe are viruses' characteristic identity. Human DNA contains 100,000 pieces of viral DNA which makes up the 8% of human genome.⁴⁶ Hemo protein, a viral protein had entered our ancestors' genomes more than 100 million years ago.⁴⁷ Viral proteins help early embryo to turn cells into any tissue as an evolutionary support by its tricks dependency.⁴⁸ Retroviral genome remnants are involved in the regulation of an essential immune functions and cellular metabolic pathways.⁴⁹ It includes HIV paired DNA inherited to next generation as Human endogenous retrovirus (HERVs), Coxsack cells, mutate and decrease the ability of viral proteins in tumours and behave like cancer. It is also a time to Make Covid-19 as an essential part of our own genetic makeup.⁵⁰

CONCLUSION

This review study suggests to approach a genetic background to know host and viral relationship and early diagnosis of an indolent infection by integrated viral genome in humans.⁵¹ Further research to get knowledge about viral persistence, its detrimental effects (death/neoplasm), low doses of hormonal replacement, gene therapy⁵¹ and an assumption of next generation sequencing is a cascade of events to overcome damage and improve survival by health measures. Immune regulating signals from retroviral genome since ancestors till date, timely selective hormone therapy application and medications are a great challenging field to dig through recent progressive science.

CONFLICTS OF INTEREST

The author and the guide declare that they have no potential conflict of interests regarding this article.

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