Does psychological stress increase fertility? Arguing rate of population growth in developing countries

Abstract

Uncontrolled population growth has raised serious concerns among future policymakers. Although fertility rate has declined substantially over time, in developing countries the rate is still very high. Most of these countries face serious issues such as; severe poverty, malnutrition, unemployment, homelessness, financial insecurity, and medical insufficiency, leading to stress and depression. This article explores the mechanisms of psychological stress and its potential effects on human fertility. An attempt is made to differfrom the existingclaim that stress is anti-steroidogenic. This counter was based onearlier studies which have asserted that individual adaptive abilities can alter the negative outcome of psychological stress depending on genetic, environmental, and behavioural factors. In conclusion, stress induced biogenesis of mitochondria may contribute in enhancing fertility. Future studies on the degree of psychological stress and its possible retaliation through subsequent adaptations would open new avenues in understanding human fertility.

Keywords: Psychological stress, Fertility rate, Mitochondrial biogenesis, Anxiety and depression

Introduction

Depending on its perception and controllability stress has both objective and subjective components.[1] It is likely that for a singlegiven stressor, individuals may react differently. Upon anticipation of a certain stressor, resulting responses are dependent on how promptly and effectively an adaptation mechanism is established. Previousreportssuggest that most chronic stresses are damaging to health and well-being;[2]whereas, acute stressesare more common and in general stimulate thrill and excitement. Most of the short periodic stresses are adaptivebut does not preclude from damages caused by sudden alteration in hormonal homeostasis.

Although stress is generally considered harmful to human health and well-being, it has also assisted in aiding the evolutionary process of adaptations. In this article, a number of facts in light of previous studiesare reviewedto support our hypothesis that, regardless of obstinate psychological stress, the astounding fertility rate in developing countries contradict the current notion of its negative impact on reproductive health and fertility.

Population growth- world perspective

The global population growth rate has never declined except for two major incidents; one, the World War II and second, the killings of 30 million people in China during 1958-1961 (Great Leap Forward). Today we count more than 7.71 billion with an estimated growth rate of 1.07% per year (www.worldometers.info/world-population). Though population growth rate has declined in the last three decades, it is assumable that the global population will continue to grow in the 21st century. Country-wise data for population growth suggests that developing countries have a much higher growth rate than developed countries.[3] The total fertility rate in developing countries, estimated at nearly 3-5% between 1995 – 2000[4]has

certainly declined compared to earlier rates but is still higher than most of the developed countries.

Why developing countries have a huge population growth rate

One of the reasons for developing countries to have a higher population growth is the absence of an effective, safe, feasible and low-costcontraceptive method.[5]Additionally,the lack of family planning,awareness, sex education andeffective government-led policies also contribute to uncontrolled population growth. Lack of equality in gender contribution towards family planning is also one of the reasons for increased population growth in developing countries. Most of these countries have patriarchal societies, thus the usability of male contraceptives is highly unlikely.[6] However, it cannot be denied that the mortality rate in all age groups are also equally high in developing countries.[7]There is also possibility of other factors that enhance the fertility rate altogether such asearly marriage, religious encouragement, parental encouragement, social influence, more time at home due tounemployment, non-working female partners, etc. In general, all the above factors are important in enhancing fertility rate in developing countries; nevertheless, the combinatorial effects of these factors are most likely to lead to stress and depression. A study by Hall et al.,[8] reported that women with higher stress and depression were more sexually active than those who were less stressed and depressed. Sexual intercourse among stressed people is also common due to its counterproductive effect of relief from tense situations.[9]

Is it true that developing nations have greater stress rate?

It is surprising that nearly 16% of the global population is affected by major depressive disorders.[10] Depression is one of the major causes of morbidity and disability in developing countries[11]. A cross-sectionalstudy reveals that nearly 35% of the sampled population of factory workers in developing countries experience anxiety, sleep disturbance,

depression, somatic complaints and various other types of stresses.[12]A study by Patel and Klienman,[13] reviewed the poverty risk relationship in developing countries. Their study explains poverty and socioeconomic statusas a few of the most influencing factors that causeemotional distress. Various factors such as income, insecurity, hopelessness, social change, education, gender, and co-morbiditywere used to establish the relationship between poverty and common mental disorders.[13]

Are stress and depression related to each other?

Reports are stating that stressful conditions such as losing jobs and loved ones, financial crisis,and insecurity cause the onset of depression.[14,15] Where depression is a key health issue affecting the quality of life, medical morbidity and mortality globally,[16,17] stress, on the other hand, is not always harmful. It is a key for survival; human evolution may not have occurred, had it not overcome subsequent stresses during critical adaptations. Worthman[18]explains 'stress' as evolutionary adaptationsagainst threats and damages to well-being. Studies show that stress has various positive effects, depending on personalities. For example, being in traffic can have differential effects on individuals, based on personality, social support, health and socioeconomic status. It is also dependent on individual conditions such asmood, self-efficacy and physical symptoms.[19-22] A study suggests that daily stressful events enhance one's response to difficult events, it also buffers one from future harmful effects of similar stressor.[23]

Mechanism of psychological stress

Stress is a complex process which causes emotional breakdown under psychological pressure or unexpected problems. It is a condition of uncomfortable emotional experiences causing biochemical, physiological and behavioural alterations.[24]Various factors influence

stress.Table 1 lists out the major factors that play important roles in physical and psychological expression of stress.

There are three physiological systems that are directly involved in psychological stress; 1) the nervous system, 2) the endocrine system and 3) the immune system.[39] Previous studies suggested that two endocrine responses are mostly responsible for negative effects of stress 1) Hypothalamic Pituitary Adrenocortical axis (HPA) and Sympathetic Adrenal Medullary (SAM).

Among all factors, the effect of diurnal cortisol is one of the important markers of psychological stress. Cortisol is a hormone produced in adrenal cortex within the adrenal gland.[40] Humans have unique diurnal cycles of cortisol levels, which measure high during mornings and low at mid-night.[41] It is responsible for the activation of HPA axis that cause inflammatory responses, metabolism of carbohydrates, lipids, proteins and gluconeogenesis. Earlier studies report that sustained stress can cause high level of circulating cortisol, creating allostatic load.[42] It is not clear; however, how chronic stress alters hypothalamic-pituitary-adrenal axis or *vice versa*.

On the other side SAM activation plays an important role in the modulation of cardiovascular, pulmonary, hepatic, skeletal muscle and immune systems. Secretion of catecholamine occurs in response to SAM activation.[43] Earlier studies reported that repeated exposure to stressful stimulus for several weeks cause numerous adaptive alterations in SAM.[44] The pattern of adaptation shown in the study carried out by McCarty et al.,[44] indicated resemblance to processes of habituation and sensitization. Prolonged activation of HPA and SAM can interfere with various physiological systems causing risk of psychological disorders.[45,46]

Apart from cortisol and catecholamine, vasopressin,[47] gonadotropin,[48,49] and insulin[50]are also regulated by psychological stress. Indirect regulation of other hormones is also related to stress, such as; growth hormone via insulin-antagonistic effect,[51,52] prolactin via level of vasopressin and peptide histidine[53]and thyroid hormone via glucocorticoids effect on central nervous system via regulation of gonadotropin.[54,55] The diagram below shows the possible manoeuvring of hormonal status during psychological stress (Figure 1).

How is stress linked to fertility?

There are various studies available which report negative impact of psychological stress on reproductive healthof both female[56-58]and male[59-61]. In females, infertility causes elevated anxiety and depression due to shame, guilt, social taunts and reduced self-esteem.[62,63] However, it is not clear if anxiety and depression cause infertility in females. In an interesting review by Rooney et al.,[64] the author claims that psychological interventions to decrease anxiety and depression lead to a significant increase in pregnancy rate.

In male, psychological stress reportedly plays an important role in reducing paternity and abnormal semen profile. The review article by Nargund[65]claims that HPA axis has a direct inhibitory action on the hypothalamic-pituitary-gonadal (HPG) axis and Leydig cells in the testis. There is ample information available that products of HPG axis modulate functions of the HPA axis.[66-68]There are also claims that mild to severe emotional stress decrease testosterone level and possibly participate in reducing spermatogenesis.[69]

Can stress increase fertility?

Arguably, even if both male and female respond negatively to psychological stress, it is difficult to deny the remarkable surge in population growth in developing countries with higher level of psychological stress. It is a valid question whether mental stress somehow acts in reverse. Or can we just for instance, assume that our interpretation of psychological stress

on reproductive health is not categorised based on the degree of successful adaptations. For example, most of the studies on psychological stress claimingadverse effect on reproductive system are based on excessive imposition of induced stress, such as; Arun et al.;[70] Gomes et al.;[71]Padoin et al.;[72] McGrady and Chakraborty[73]etc. These studies possibly do not replicate the actuality of human psychological stress entirely, as stress is a complex process and one of the keys to survival. Stressors have deleterious effects on the cellular processes, nonetheless, simultaneously it encourages various adaptive responses to reduce damages and maintain normalcy in the cell. Mitochondria is considered a key organelle that responds to stresses, such as; 'fight and flight response' by maintaining a huge amount of energy demand.[74,75] In contrast to a study carried out by McGrady,[69] a study by Gak et al.,[76] reports that psychological stress triggers mitochondrial biogenesis which encourages adaptive mechanism in testosterone producing Leydig cells.

The study by Gak et al.,[76] also reports that acute stress activates PGC1 protein that is required for the production of new mitochondria and assist against oxidative stress related damages. Previous studies claim that the activity of mitochondria (mitochondrial protein import machinery and mitochondrial fusion) is important for steroid genesis in Leydig cells.[77-82]Interestingly, mitochondria also play an important role in male fertilization. Mitochondria of the spermatozoa are tightly wrapped around the axoneme, at the mid-piece.[83] These power plants are vital for sperm motility and to ensure male fertility. Hyperactivated motility at the site of fertilization is dependent on mitochondria for an adequate supply of energy that is utilized by the flagellar dynein-ATPase.[84,85] A detailed review by Piomboni et al.,[86] on the role of mitochondria in sperm motility, concluded by suggesting that deeper study on mitochondrial functions will open new possibilities to understand bioenergetics of sperm mitochondria and fertility. It is interesting to note that a typical mammalian sperm mid-piece contains 50-75 mitochondria, whereas, the mammalian oocyte contains around

10^5-10^8 mitochondria.[87]The numbers of mitochondria in both sperms and oocytes indicate a high demand of energy for successful fertilization. Thus, the production of new mitochondria can invariably support fertilization.

Conclusion

Stress can be both adaptive and threatening depending on various factors such as; genetic, behavioural and environmental. These factors individually or in combination provide adaptive coping resources to individuals. Any positive adaptive ability is a process of refinement in the course of evolution. This article concludes that adaptable psychological stress can affect fertility, completely oppositeto anxiety and depression. Therefore, it is possible that human reproducibility may increase in a stressful environment through mitochondrial biogenesis. Nevertheless, there is more to be explored, for better understanding ofrole of stress in human fertility.

References

1. Koolhaas JM, Bartolomucci A, Buwalda B de Boer SF, Flugge G Korte SM, et al. Stress revisited: a critical evaluation of the stress concept. *NeurosciBiobehav Re*v.,**35**(5): 1291-01 (2011).
2. Mariotti A. The effects of chronic stress on health: new insights into the molecular mechanisms of brain-body communication. *Future Sci OA.*,**1**(3): FSO23 (2015).
3. Population Facts, Accelerating achievement of the MDGs by lowering fertility: Overcoming the challenges of high population growth in the least developed countries. Department of Economic and Social Affairs, Population Division, United Nations. 2010.
4. Desai V, Potter R (Eds.). The Arnold Companion to development studies, London, UK: *Hoddar Arnold.*, p.360-67. (2002).
5. Lohiya NK, Alam I, Hussain M, Khan SR, Ansari AS. RISUG: an intravasal injectable male contraceptive. *Indian J Med Res.*,**140**(S1): 63-72 (2014).
6. Lohiya NK, Alam I, Ansari AS. In Basic of Andrology (EDS.) Kumar ATN, Sharma M. *Springer Nature*, Singapore. p. 493-508. (2017).
7. United Nations, Department of Economic and Social Affairs, Population Division (2017). World Mortality: Data Booklet. New York: United Nations. (2017).
8. Hall KS, Kusunoki Y, Gatny H, Barber J. Stress symptoms and frequency of sexual intercourse among young women. *J Sex Med*.,**11**(8): 1982-90 (2014).
9. Ein-Dor T, Hirschberger G. Sexual healing: Daily diary evidence that sex relieves stress for men and women in satisfying relationships. *J Soc Pers Relatsh.*,**29**(1): 126-39 (2012).
10. Kessler RC, Berglund P, Demler O, Jin R, Koretz DMerikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA.*,**289**(23): 3095-105 (2003).
11. Abas M, Broadhead J. Mental disorders in the developing world. *BMJ.*,**308**: 1052 (1994).

12. Shankar J, Famuyiwa OO. Stress among factory workers in a developing country. *J Psychosom Res.*,**35**(2-3): 163-71 (1991).
13. Patel V, Kleinman A. Poverty and common mental disorders in developing countries. *Bull World Health Organ*.,**81**(8): 609-15 (2003).
14. Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature.*,**455**(7215): 894-902 (2008).
15. Uchida S, Hara K, Kobayashi A, Otsuki K, Yamagata H Hobara T, et al. Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. *Neuron*.,**69**(2): 359-72 (2011).
16. Spijker J, Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. Functional disability and depression in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Acta Psychiatr Scand*.,**110**: 208-14 (2004).
17. Ustuun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. *Br J Psychiatry*.,**184**: 386-92 (2004).
18. Worthman CR. Basics in Human Evolution. Chapter- 32 *Evolutionary Biology of Human Stress*., p.441-53. (2015).
19. Affleck G, Tennen H, Urrows S, Higgins P. Person and Contextual Features of Daily Stress Reactivity: Individual Differences in Relations of Undesirable Daily Events With Mood Disturbance and Chronic Pain Intensity. *J Pers Soc Psychol*.,**66**(2): 329-40 (1994).
20. Almeida DM. Resilience and vunerability to daily stressrs assessed via diary methods. *Curr Dir Psychol Sci*.,**14**(2): 64-8 (2005).
21. Chamberlin K, Zika S. The minor events approach to stress: Support for the use of daily hassles. *Br J Psychol*., **81**(4)*:* 469-81 (1990).
22. Tennen H, Affleck G, Armeli S, Carney MA. A Daily Process Approach to Coping. *Am Psychol*.,**55**(6): 626-36 (2000).

23. Donald J, Atkins PWB, Parker PD, Christie AM. Daily stress and the benefits of mindfulness: Examining the daily and longitudinal relations between present-moment awareness and stress responses. *J Res Pers*.,**1**: 192 (2016).
24. Baum A. Stress, intrusive imagery, and chronic distress. *Health Psychol*.,**9**(6): 653-75 (1990).
25. Katz DA, Sprang G, Cooke C. The cost of chronic stress in childhood: Understanding and applying the concept of allostatic load. *Psychodyn Psychiatry*.,**40**(3): 469-80 (2012).
26. Koffer RE, Ram N, Conroy DE, Pincus AL, Almeida DM. Stressor diversity: Introduction and empirical integration into the daily stress model. *Psychol Aging*.,**31**(4): 301-20 (2016).
27. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE Morrow JD, et al. Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci USA*.,**101**(49): 17312-15 (2004).
28. Price LH, Kao HT, Burgers DE, Carpenter LL, Tyrka AR. Telomeres and early-life stress: An overview. *Biol Psychiatry*.,**73**(1): 15-23 (2013).
29. Shalev I, Entringer S, Wadhwa PD, Wolkowitz OM, Puterman E Lin J, et al. Stress and telomere biology: A lifespan perspective. *Psychoneuroendocrinology*.,**38**(9): 1835-42 (2013).
30. Gouin J, Glaser R, Malarkey WB, Beversdorf D, Kiecolt-Glaser J. Chronic stress, daily stressors, and circulating inflammatory markers. *Health Psychol*.,**31**(2): 264-68 (2012).
31. Barker ET, Greenberg JS, Seltzer MM, Almeida DM. Daily stress and cortisol patterns in parents of adult children with a serious mental illness. *Health Psychol*.,**31**(1): 130-34 (2012).
32. Arnsten AFT. Stress signalling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci*.,**10**(6): 410-22 (2009).

33. Gold PW. The organization of the stress system and its dysregulation in depressive illness. *Mol Psychiatry*.,**20**: 32-47 (2015).

34. Mika A, Mazur GJ, Hoffman AN, Talboom JS, Bimonte-Nelson HA Sanabria F, et al. Chronic stress impairs prefrontal cortex-dependent response inhibition and spatial working memory. *BehavNeurosci*.,**126**(5): 605-19 (2012).

35. Brown ES, Jeon-slaughter H, Lu H, Jamadar R, Issac S Shad M, et al. Hippocampal volume in healthy controls given 3-day stress doses of hydrocortisone. *Neuropsychopharmacology*.,**40**: 1216-21 (2015).

36. Roozendaal B, Mcewen BS, Chattarji S. Stress, memory and the amygdala. *Nat Rev Neurosci*.,**10**(6): 423-33 (2009).

37. Head D, Singh T, Bugg JM. The moderating role of exercise on stress-related effects on the hippocampus and memory in later adulthood. *Neuropsychology*.,**26**(2): 133-43 (2012).

38. Weller JA, Buchanan TW, Shackleford C, Morganstern A, Hartman JJ. Diurnal cortisol rhythm is associated with increased risky decision-making in older adults. *Psychol Aging*.,**29**(2): 271-83 (2014).

39. Everly G. Physiology of stress. In: Brian, B.S., Seaward, L. (Eds.), Managing Stress: Principles and Strategies for Health and Wellbeing. Jones and Bartlett Publishers, Canada, p. 34-48 (2006).

40. Scott E. Cortisol and Stress: How to Stay Healthy. (2011). (http://stress.about.com/od/stresshealth/a/cortisol.htm).

41. Martin PA, Crump MH. The adrenal gland. In Dooley MP, Pineda MH (eds.): McDonald's veterinary endocrinology and reproduction (5th ed.). Ames, Iowa: Iowa State Press (2003).

42. Braveman P, Gottlieb L. The social determinants of health: it's time to consider the causes of the causes. *Public Health Rep*.,**129**(2): 19-31 (2014).

43. Moreno-Villanueva M, Bürkle A. Molecular consequences of psychological stress in human aging. *Exp Gerontol*., ***68***: 39-42 (2015).

44. McCarty R1, Horwatt K, Konarska M. Chronic stress and sympathetic-adrenal medullary responsiveness. *Soc Sci Med*.,**26**(3): 333-41 (1988).

45. Cohen S, Kessler RC, Gordon UL. Strategies for measuring stress in studies of psychiatric and physical disorder. In: Cohen, S., Kessler, R.C., Gordon, U.L. (Eds.), Measuring Stress: A Guide for Health and Social Scientists. Oxford University Press, New York, NY, p. 3-26 (1995).

46. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*.,**338**(3): 171-79 (1998).

47. Aguilera G, Subburaju S, Young S, Chen J. The parvocellular vasopressinergic system and responsiveness of the hypothalamic pituitary adrenal axis during chronic stress. *Prog Brain Res*.,**170**: 29-39 (2008).

48. Cameron JL. Stress and behaviorally induced reproductive dysfunction in primates. *Semin Reprod Endocrinol*.,***15***: 37-45 (1997).

49. Lachelin GC, Yen SS. Hypothalamic chronic anovulation. *Am J Obstet Gynecol*.,**130**: 825-31 (1978).

50. Halter JB, Beard JC, Porte D Jr. Islet functions and stress hyperglycemia: Plasma glucose and epinephrine interaction. *Am J Physiol*.,**247**: 47-52 (1984).

51. Delitala G, Tomasi P, Virdis R. Prolactin, growth hormone and thyrotropinthyroid hormone secretion during stress in man. *Baillieres Clin EndocrMetab*.,**1**: 391-414 (1987).

52. Skuse D, Albanese A, Stanhope R, Gilmour J, Gilmour L. A new stress related syndrome of growth failure and hyperphagia in children, associated with reversibility of growth hormone insufficiency. *Lancet*.,**348**: 353-58 (1996).

53. Itoh N, Obata K, Yanaihara N, Okamoto H. Human prepro vasoactive intestinal polypeptide contains a novel PHI27like peptide, PHM27. *Nature*.,**304**: 547-49 (1983).

54. Helmreich DL, Parfitt DB, Lu XY, Akil H, Watson SJ. Relation between the hypothalamic pituitary thyroid (HPT) axis and the hypothalamic pituitary adrenal (HPA) axis during repeated stress. *Neuroendocrinology*., **81**: 183-92 (2005).

55. Calogero AE, Burrello N, Bosboom AM, Garofalo MR, Weber RF D'Agata R. Glucocorticoids inhibit gonadotropin-releasing hormone by acting directly at the hypothalamic level. *J Endocrinol Invest*.,**22**(9): 666-70 (1999).

56. Maroufizadeh S, Navid B, Omani-Samani R, Amini P. The effects of depression, anxiety and stress symptoms on the clinical pregnancy rate in women undergoing IVF treatment. *BMC Res Notes*.,**12**(1): 256 (2019).

57. Zhou FJ, Cai YN, Dong YZ. Stress increases the risk of pregnancy failure in couples undergoing IVF. *Stress*.,**22**(4): 414-20 (2019).

58. Merklinger-Gruchala A, Kapiszewska M. The Effect of Prenatal Stress, Proxied by Marital and Paternity Status, on the Risk of Preterm Birth. *Int J Environ Res Public Health*.,**16**(2): 273 (2019).

59. Ilacqua A, Izzo G, Emerenziani GP, Baldari C, Aversa A. Lifestyle and fertility: the influence of stress and quality of life on male fertility. *ReprodBiol Endocrinol*.,**16**(1): 115 (2018).

60. Durairajanayagam D. Lifestyle causes of male infertility. *Arab J Urol*.,**16**(1): 10-20 (2018).

61. Prastyo DB, Deliana M, Dimyati Y, Arto KS. The Effect of Psychological Stress on Salivary Testosterone in Puberty Children. Open Access *Maced J Med Sci*.,**6**(9): 1611-16 (2018).

62. Domar AD, Zuttermeister PC, Friedman R. The psychological impact of infertility: a comparison with patients with other medical condition. *J PsychosomObstetGynaecol*.,**14**(l): 45-52 (1993).

63. Fast Facts About Infertility. Available at: http://www.resolve.org/ about/fast-facts-about-fertility.html. Resolve: The National Fertility Association (2017).

64. Rooney KL, Domar AD. The relationship between stress and infertility. *Dialogues Clin Neurosci*.,**20**(1): 41-47 (2018).

65. Nargund VH. Effecys of psychological stress on male fertility. *Nat Rev Urol*.,**12**(7): 373-82 (2015).

66. Viau V, Meaney MJ. The inhibitory effect of testosterone on hypothalamic-pituitary-adrenal responses to stress is mediated by the medial preoptic area. *J Neurosci: Society for Neuroscience*.,**16**(5): 1866-76 (1996).

67. Viau V. Functional cross-talk between the hypothalamic-pituitary-gonadal and -adrenal axes. *J Neuroendocrinol*.,**14**(6): 506-13 (2002).

68. Seale JV, Wood SA, Atkinson HC, Harbuz MS, Lightman SL. Gonadal steroid replacement reverses gonadectomy-induced changes in the corticosterone pulse profile and stress-induced hypothalamic-pituitary-adrenal axis activity of male and female rats. *J Neuroendocrinol*.,**16**(12): 989-98 (2004).

69. McGrady AV. Effects of psychological stress on male reproduction: a review. *Arch Androl*.,**13**(1): 1-7 (1984).

70. Arun S, Burawat J, Sukhorum W, Sampannang A, Uabundit N Iamsaard S. Changes of testicular phosphorylated proteins in response to restraint stress in male rats. *J Zhejiang Univ Sci B.*,**17**(1): 21-29 (2016).

71. Gomes CM, Raineki C, Ramos de Paula P, Severino GS, Helena CVAnselmo-Franci JA et al. Neonatal handling and reproductive function in female rats. *J Endocrinol*.,**184**(2): 435-445 (2005).

72. Padoin MJ, Cadore LP, Gomes CM, Barros HM, Lucion AB. Long-lasting effects of neonatal stimulation on the behavior of rats. *BehavNeurosci*.,**115**(6): 1332-40 (2001).

73. McGrady AV, Chakraborty J. Effects of stress on the reproductive system of male rats and mice. *Arch Androl*.,**10**(2): 95-101 (1983).

74. Dym M, Fawcett DW. Observations in the blood testis barrier of the rat and on the physiological compartmentation of the seminiferous epithelium. *BiolReprod*.,**3**: 308-26 (1970).

75. Meinhard E, McRae CV, Chisholm GE. Testicular biopsy in evaluation of male infertility. *Br Med J*.,**3**: 577 (1973).

76. Gak IA, Radovic SM, Dukic AR, Janjic MM, Stojkov-Mimic NJ Kostic TS, et al. Stress triggers mitochondrial biogenesis to preserve steroidogenesis in Leydig cells. *BiochimBiophys Acta*.,**1853**(10): 2217-27 (2015).

77. Allen JA, Shankara T, Janus P, Buck S, Diemer T Hales KH, et al. Energized, polarized and actively respiring mitochondria are required for acute Leydig cell steroidogenesis. *Endocrinology*.,**147**: 3924-35 (2006).

78. Haider SG. Leydig cell steroidogenesis: unmasking the functional importance of mitochondria. *Endocrinology*.,**148**: 2581-82 (2007).

79. Midzak AS, Chen H, Aon MA, Papadopoulos V, Zirkin BR. ATP synthesis, mitochondrial function, and steroid biosynthesis in rodent primary and tumor Leydig cells. *BiolReprod*.,**84**: 976-85 (2011).

80. Poderoso C, Duarte A, Cooke M, Orlando U, Gottifredi V Solano AR, et al. The spatial and temporal regulation of the hormonal signal. Role of mitochondria in the formation of a protein complex required for the activation of cholesterol transport and steroids synthesis. *Mol Cell Endocrinol*.,**371**: 26-33 (2013).

81. Duarte A, Poderoso C, Cooke M, Soria G, Cornejo Maciel F Gottifredi V, et al. Mitochondrial fusion is essential for steroid biosynthesis. *PLoS One*.,**7**: 45829 (2012).

82. Duarte A, Castillo AF, Podesta EJ, Poderoso C. Mitochondrial fusion and ERK activity regulate steroidogenic acute regulatory protein localization in mitochondria. *PLoS One*.,**9**: 100387 (2014).

83. Eddy EM, Toshimori K, O'Brien DA. Fibrous sheath of mammalian spermatozoa. *Microsc Res Tech*.,**61**: 103-15 (2003).

84. Ford WC. Glycolysis and sperm motility: does a spoonful of sugar help the flagellum go round? *Hum Reprod Update*.,**12**: 269-74 (2006).

85. Turner RM. Moving to the beat: a review of mammalian sperm motility regulation. *Reprod Fertil Dev*.,**18**: 25-38 (2006).

86. Piomboni P, Focarelli R, Stendardi A, Ferramosca A, Zara V. The role of mitochondria in energy production for human sperm motility. *Int J Androl*.,**35**(2): 109-24 (2012).

87. Piko L, Matsumoto L. Number of mitochondria and some properties of mitochondrial DNA in the mouse egg. *Dev Biol*.,**4**: 1-10 (1976).

Table 1: List of psychological stress associated factors

Factors		References
Environmental factors		
Chronic stressors	Allostatic load	25
Stressor diversity	High diversity lead to high negative impact	26
Physiological factors		
Telomeres	Shortening of telomeres is associated with stress	27-29
Circulating inflammatory markers	Interleukin 6 and C-reactive protein	30
Electrodermal activity	Hypo-activation of diurnal cortisol	31
Attention and memory		
Prefrontal cortex	Negative impact (Psychological stress triggers release of noradrenaline and dopamine)	32-34
Hippocampus	Negative impact (Reduced volume) (triggers release of glucocorticoids)	35-37
Decision making	Diurnal cortisol rhythm	38

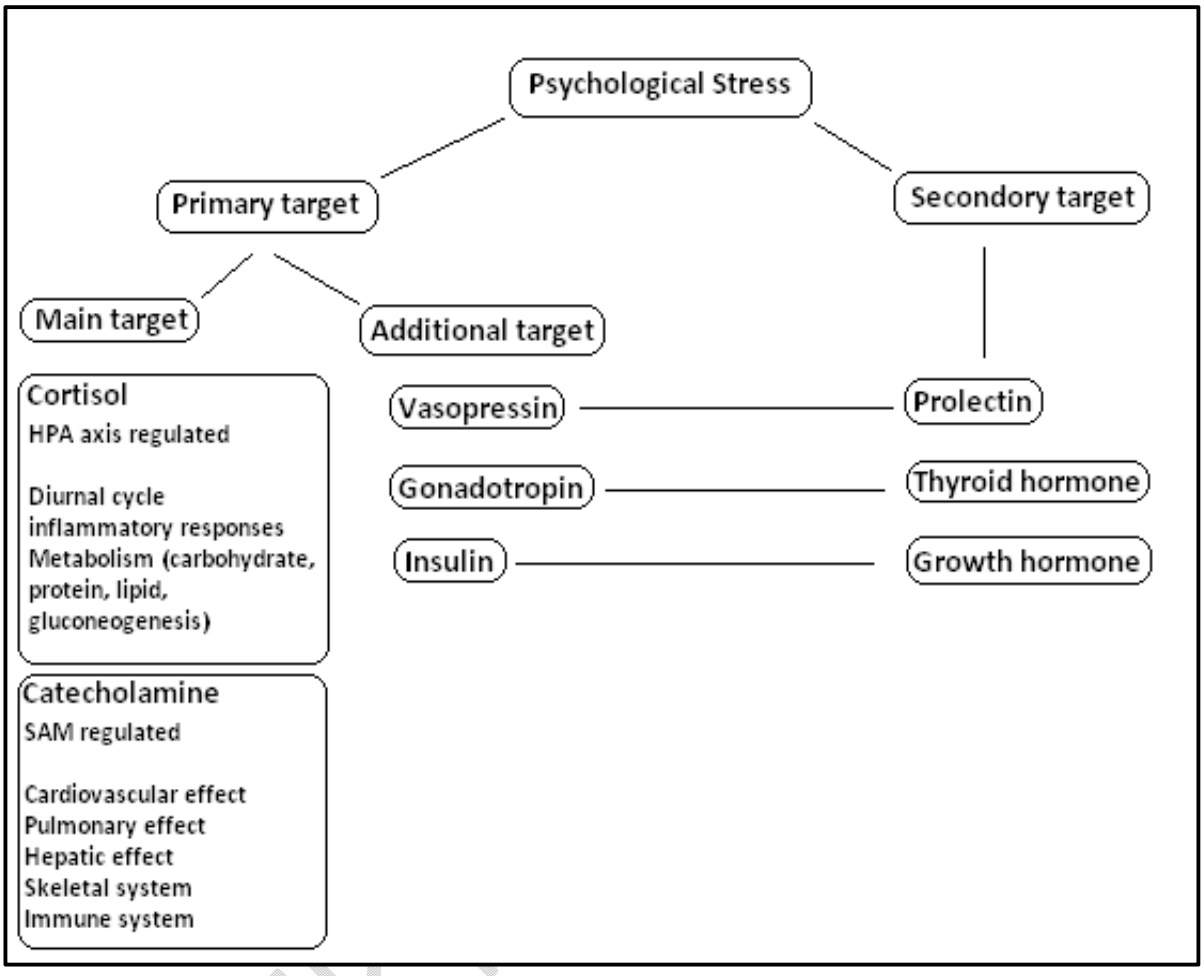

Figure 1: Diagram shows possible targets of psychological stress and its consequential metabolic effect.