BRIEF COMMUNICATION

Nonlinear Dynamics of Endocrine Feedback in Hypothalamico-Pituitary-Ovarian (HPO) Axis and Its Prospective Role in Screening and Understanding Etiology of Ovarian Cancer

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Abstract

The idea of feedback mechanisms in endocrine medicine has remained ill conceived especially in the light of modern control theory where energy transfer is understood in a system wise fashion. The idea is based on reductionism i.e. describing function on a discrete molecular level whilst at the macro level the desired accuracy is not achieved.

Endocrinology text books have even gone with this wind of discreteness, some have even drastically cut the subject to a bare minimum probably agreeing to the sanctity of its omnipotence. End product inhibition, regulatory enzymes, allosteric configuration changes and other physiological phenomena are examples of biological feedback mechanisms. It is not astonishing that modern control theory with all its mathematical facets has already gained a perceptible entry into the endocrinology literature. Applications of chaos theory in gynaecology and obstetrics were proposed in the early nineteen-eighties.

Applications of biomathematics including nonlinear control theory is fast gaining ground and, like molecular biology in last decade can not be ignored anymore. For our understanding of hormone function to progress, endocrinological feedback mechanisms as part of gynaecological and obstetric assessment needs to be understood within complex systems science.

Keywords: endocrine feedback, dynamical system, Lyapunov exponent, nonlinearity, ovarian cancer

Özet

Hipotalamus-Hipofiz-Over (HHO) Aksında Endokrin Geribeslemenin Non-Lineer Dinamiği ve Bunun Over Kanserini Tarama ve Etiyolojisini Anlamadaki Prospektif Rolü

Özellikle enerji transferinin sisteme dayalı bir şekilde görüldüğü modern kontrol teknolojisinin ışığında bakıldığında, endokrin tıpta geribesleme mekanizması fikrine hâlâ şüpheyle bakılmaktadır. Bu fikir redüksiyonizme, yani makro seviyede arzulanan titiz ölçüm değerlerine ulaşılamazken, fonksiyonu belirsiz moleküler seviyede tanımlamaya dayanmaktadır. Endokrinoloji kitapları bu belirsizlik akımına kapılmakla kalmayıp, bazıları belki de bu akımın her şeye kadir kutsallığını onayladıklarından, geribesleme mekanizması fikrine gerekli önemi vermemişlerdir. Son ürün inhibisyonu, düzenleyici enzimler, allosterik dizilim değişiklikleri ve diğer fizyolojik fenomenler biyolojik geribesleme mekanizma örnekleridir. Tüm matematiksel boyutlarıyla ele alındığında, modern kontrol teorilerinin endokrinoloji literatürüne kayda değer bir şekilde girmesi şaşırtıcı değildir. Kaos teorisinin jinekoloji ve obstetrikte uygulanması 80'lerin başında önerilmiştir. Non-lineer kontrol teorisini içeren biyomatematik uygulamalar hızla yaygınlaşmaktadır ve son 10 yılda moleküler biyolojide olduğu gibi, artık göz ardı edilemez. Hormon fonksiyonlarını daha iyi anlayabilmemiz için jinekolojik ve obstetrik değerlendirmenin bir bölümü olarak endokrinolojik geribesleme mekanizmalarının kompleks sistem bilimi kapsamında anlaşılması gerekir.

Anahtar sözcükler: endokrin geribesleme, dinamik sistem, Lyapunov öğesi, non-lineerlik, over kanseri

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Introduction

Endocrine feedback system may not be appreciated by conventional hormone level estimation at a single point of time. Wide fluctuations, diurnal oscillation hardly follows linear relationship and model. Nonlinear model is far more efficient to deal with random looking data. Linear multiple regression model sometimes fails to predict and analyze data. Before declaring data as random, nonlinear modeling will be necessary to define the data. Our body also needs to be looked at as a dynamic system, a dissipative structure (1) with stability outside equilibrium as Ilya Prigogine, the Nobel laureate, called it. Specially, a science that is not random but deterministic (2,3) must guide the information processing at neuroendocrine level. Calculation of Lyapunov exponent (λ) (5), which is described as sensitivity to initial condition, helps to determine whether data is random or deterministic. For sustenance of life, body environs must always (at present moment) balance itself delicately and relentlessly. In this dynamic system feedback control will essentially be mathematical control that has to be understood in the light of physical control theory (4,5). Likewise, endocrine reaction and resultant hormone or receptor levels that will follow Michaelis-Menten-Hill kinetics can be looked at as signal that moves in the phase space of our body and can be plotted in graph that can be digitized and analyzed using nonlinear science (6,7). Though image processing and texture (8,9) screening is done using nonlinear complexity science, or chaos theory, as we call it, this signal of reaction kinetics with changing hormone levels may be looked as a vector running in phase space of our body milleu against time. Its trajectory can be calculated in an n dimensional context which will require mathematical and statistical manipulation to bring in two dimensional graph. This graph then will be used to detect some fractal dimension after such normalization as is necessary. Those dimensions can judge whether the same kinetics of two separate body system will coincide or differ. This can be used to differentiate disease state from normal state. Thus positive and negative feedback may be more rationally and mechanically explained. More definitive biochemical knowledge and prediction will then be possible. Fractal geometry and nonlinear chaos has proven to be very much useful tool in quantifying the structure of idealized and naturally occurring metabolism. Nonlinear estimation has tremendous impact in almost all subject from pure mathematics, through physics and chemistry, to biology and medicine. Many processes of normalization of data such as Fourier transform, and capacity dimension are described which are used to 'smoothen' craggyness of data in graph. A hypothalamo-pituitary ovarian axis and ovarian cancer is taken up as example to use this science for better understanding of ovarian cancer aetiopathology.

Materials and Methods

Basic calculations

To elucidate the unknown mechanism of pulsatile follicle stimulating hormone (FSH) release in three distinct different phases of premenopausal proliferative, premenopausal secretary phases and postmenopausal period we have to construct a number of physiologically consistent models with an empirically determined input-output relation. All models must have a parametrically equivalent basis i.e. be able to explain life events with uniformity of rationale. As the dynamical property of the pituitary gland, which secretes FSH, is largely unknown some modification may be needed at that level. First the MM equation is to be solved analytically to obtain a solution of the mean equifinal intermediate hormone levels. From these results a computer simulation that includes computational loops for binding hormone to receptor and plasma protein can generate a time series of the respective hormone levels. To model the HPO axis for FSH we can apply the MM equations and combine these in the feedback equation from three equations as below [Equation 1].

In pituitary gonadotrophin releasing hormone (GnRH) [Equation 2] will have temporal pattern of release into the hypothalamic pituitary portal vessels. An ultra-short feedback loop connecting FSH to the pituitary is also taken into account. Non competitive inhibition of FSH release by receptor bound oestrogen ($[E]_R$) could be expressed as

$$\frac{d[FSH]}{dt} = \frac{\alpha_S G_h [GnRH]_0}{(D_H+[GnRH]_0)(1+L_S[E]_R)} - \beta_S[FSH] \quad \ldots (1)$$

$[GnRH]_0$ is the GnRH level in the pituitary stalk vessel and with ultra short feedback loop of FSH in the pituitary $[FSH]_z$ effects its own release according to

$$\frac{d[FSH]}{dt} = \frac{\alpha_S G_h [GnRH]_0}{(D_H+[GnRH]_0)(1+L_S[E]_R) Z} - \beta_S[FSH] \quad \ldots (2)$$

$$\text{where} \quad Z = \left(1 + \frac{S_S[FSH]_Z}{D_S+[FSH]_Z}\right) \quad \ldots(3)$$

Where G_h= Secretion capacity of pituitary
D_H=damping constant of GnRH in pituitary
D_S=damping constant of FSH in pituitary
α_S=dilution factor of FSH
β_S=clearance exponent of FSH
S_S=brake constant of FSH ultra short feedback
L_S=damping constant of FSH in ovary

Discussion

Our job now will be to define feedback process here and to see whether chaos is behind maintenance of female physiology by observing nature of oscillation of hormone levels in light of modern nonlinear control.

One may expect that the solution of equations would be hyperchaotic or random ($\lambda<0$) and there may be more than one Lyapunov exponents (10), which are greater than zero. Contrarily, there could be only one positive Lyapunov exponent, i.e., the solutions of equations are not hyperchaotic but nonlinear deterministic.

If chaotic solution were presumed we may proceed to calculate correlation dimension using box-counting theorem or capacity dimension in normal and diseased patient (i.e. patient with ovarian cancer) (11,12). Then by measuring oscillation and levels of different hormones over a few days it might be possible to predict if one particular woman may suffer from this cancer or not so that some preventive measures can be taken.

In recent studies, serum follicle stimulating hormone (FSH) levels in postmenopausal epithelial ovarian cancer patients were found to be significantly lower (13-15), even in preclinical phase of the disease (16). Levels of luteinizing hormone (LH) were found unchanged in those studies. Since ovulation is intrinsically linked to gonadotrophin stimulation, regulation of gonadotrophin stimulation and gonadotrophin receptors (FSHR & LHR) may be important in such cancers. By repeated experiments the cause that leads to a lowering of the FSH level could not be ascertained. As a result gonadotrophin theory itself suffers a setback. Gonadotrophin releasing hormone (GnRH) agonist, triptorelin, has failed earlier to produce any relevant beneficial effect in patients with advanced ovarian cancer who received standard surgical cytoreduction and cytotoxic chemotherapy in a fairly large prospective double blind randomized trial (17). While evidence is conflicting, a critical role for gonadotrophins in the genesis and progression of ovarian cancer cannot be ruled out, especially where a high FSHR expression is found to be assoiated with the ovarian surface epithelium and low level of FSH in blood. It seems lucrative to think that these two phenomena have a common and important relation in causation of such cancer. However, it is not possible to comment on this before both FSH and FSHR are tested in same set of experiments. There are a few studies of the receptors in epithelial ovarian cancer (18-21). Investigating the role of receptors other than the receptors for GnRH, gonadotrophin and sex steroids in endocrine feedback and searching for the cause of aberrant expression of FSHR in epithelial cells seems worthwhile.

Hence, simulated and real time series of HPO axis hormone levels as described in the section on biochemical reaction kinetics can be processed and interpreted by calculating the fractal dimensions of the signal patterns.

The first measure of complexity used is the fractal capacity dimension D_{cap}. This approach covers the graphical representation of the time series with squares of successively varied border length e [Equation 3]. For each length it counts the number N(e) of squares covering the curve. With

$$D_{cap} = \lim_{t \to \infty} \frac{\log N(e)}{\log 1/e} \quad \text{..... (4)}$$

The capacity dimension can be calculated and compared for real (premenopausal proliferative, premenopausal secretary, postmenopausal normal and postmenopausal epithelial ovarian cancer cases) and simulated time series.

By means of the second approach to determine the data's complexity the so-called correlation dimension, which however is not ideal [Equation 4].

Real time series of four conditions as mentioned above (premenopausal proliferative, premenopausal secretary, postmenopausal normal and postmenopausal epithelial ovarian cancer cases) can thus be compared among them and with that generated from models. Both capacity dimension and correlation dimension can now be calculated with software available on the World Wide Web (http://astronomy.swin.edu.au/pbourke/fractals/fracdim/, http://link.medinn.med.uni-muenchen.de/cybermed/nonlin/cd2/).

Using nonlinear analysis it may be possible to determine the reason for the aberrant expression of FSHR in epithelial ovarian cancer. Utilizing the different methods described for differentiating the real time series we can compare which of them is most sensitive. This was done before in differentiating cancer from normal cases using multivariate analysis (11). Here the discriminant function, Z was superior to Mahalanabis Distance.

Further deduction (function of function of function etc.) takes us to the end of modern physical control and by repeating (iterating) function infinitesimally we get fractal dimensions and graphics for efficient differentiation.

References

1. Stein DL. Dissipative structures, broken symmetry, and the theory of equilibrium phase transitions, J Chem Phys 72:2869-74.
2. Abarbanel HDI, Brown R, Sidorowich JJ, and Tsimring LShT. The analysis of observed chaotic data in physical systems, Rev. Modern Physics 1993; 65:1331-92.
3. Jeong J, Gore JC, Peterson BS. A method for determinism in short time series, and its application to stationary EEG. IEEE Trans Biomed Eng 2002 Nov;49(11):1374-9.
4. Packard NH, Crutchfield JP, Farmer JD, and Shaw RS. Geometry from a time series, Phys Rev Lett 1980;45, no. 9:712.
5. Eckmann JP, Kamphorst SO et al. Liapunov exponents from time series. Phys Rev 1986;A 34:4971-9.
6. Saratchandran P, Carson ER and Reeve J. An improved mathematical model of human thyroid hormone regulation. Clinical Endocrinology 1976; 5:473-83.
7. Li G, Liu B and Liu Y. A dynamical model of the pulsatile secretion of the hypothalamo-pituitary-thyroid axis. Biosystems 1995;35(1):83-92.
8. Nielsen B, Albregtsen F, Kildal W, Danielsen HE. Prognostic classification of early ovarian cancer based on very low dimensionality adaptive texture feature vectors from cell nuclei from monolayers and histological sections. Anal Cell Pathol 2001;23(2):75-88.
9. Brincat MP. Chaos theory in obstetrics and gynaecology. Br J Obstet Gynaecol 1994;101(11):931-4.
10. Lyapunov MA. Problème général de la stabilité du mouvement. Ann Fac Sci Toulouse 1907; vol 9, pp. 203-474 (Translation of the original paper published in 1892 in Comm Soc Math Kharkow and reprinted as Vol. 17 in Ann Math Studies, Princeton University Press, Princeton, N.J. 1949).
11. Bose CK & Mukherjea M. Enzymatic tumour markers in ovarian cancer: a multiparametric study. Cancer Lett 1994;77(1):39-43.
12. Bose CK, Sarkar B et al. 2004. Dynamics of endocrine feedback. http://www.iscid.org/boards/ubb-get_topic-f-26-t-000004.html
13. Blaakaer J, Djursing H et al. The pituitary gonadal axis in women with benign or malignant ovarian tumours. Acta Endocrinologica 1992;127:127-30.

14. Menon U, Riley SC, Thomas J et al. Serum inhibin, activin, follistatin in postmenopausal women with epithelial ovarian cancer. British Journal Obstetrics & Gynaecology 1999;107:1069-74.
15. Bose CK, Menon U, Thomas J et al. Gonadotrophin levels in postmenopausal women with epithelial ovarian cancer. Journal Obstetrics & Gynaecology of India 2001; 51, No. 6.
16. Helzlseour KJ , Alberg AJ et al. Serum gonadotrophins and steroid hormone and the development of ovarian cancer. Journal of American Medical Association 1995;274;1926-30.
17. Emons G, Ortmann O, Teichert HM et al. Luteinising hormone releasing hormone agonist triptorelin in combination with cytotoxic chemotherapy in patients with advanced ovarian carcinoma. A prospective double blind randomized trial. Decapeptyl ovarian cancer study group. Cancer 1996;78(7):1452-60.
18. Parrott JA, Doraiswamy V, Kim G et al. Expression and actions of both the follicle stimulating hormone receptor and the luteinizing hormone receptor in normal ovarian surface epithelium and ovarian cancer. Molecular Cellular Endocrinology 2001;172(1-2):213-22.
19. Zheng W, Lu JJ, Luo F et al. Ovarian epithelial tumor growth promotion by follicle-stimulating hormone and inhibition of the effect by luteinizing hormone. Gynecol Oncol 2000;76:80-8.
20. Wang J, Lin L, Parkash V et al. Quantitative analysis of follicle-stimulating hormone receptor in ovarian epithelial tumors: a novel approach to explain the field effect of ovarian cancer development in secondary mullerian systems. Inter Journal of Cancer 2003;103(3):328-34.
21. Mandai M, Konishi I, Kuroda H et al. Messenger ribonucleic acid expression of LH/hCG receptor gene in human ovarian carcinomas. European Journal of Cancer 1997 Aug;33(9):1501-7.