

Full Length Research paper

Role of catecholamine in tumor angiogenesis linked to capacitance relaxation phenomenon

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The present paper describes the role of catecholamine with chromogranin A (CgA) in tumor angiogenesis linked to capacitance relaxation phenomenon. The capacitance relaxation phenomenon is the observation about the capacitance value which jumps rapidly in cancer cell around 200Hz. It has been established that catecholamine is of recent interest in regulation of angiogenesis. The present paper deals with chromogranin A (CgA), coreleased with catecholamine in plasma in patients suffering from pheochromocytoma (PHEO), multiple endocrine neoplasia (MEN), medullary thyroid carcinoma (MTC), and congenital adrenal hyperplasia (CAH) and patients with others endocrine disorders. The paper also discusses the progressive rise in CgA with catecholamine linked to capacitance relaxation phenomenon. The experimental results of capacitance relaxation phenomenon were given as inputs to a model for correlation with the CgA level and catecholamine. It is to be noted that the model is simulated in MATLAB 7.0. MATLAB allows matrix manipulations, plotting of functions and data, implementation of algorithms, creation of user interface and interfacing with programs written in other languages.

Keywords: Chromogranin A, capacitance relaxation phenomenon, catecholamine, tumorigenesis.

INTRODUCTION

Catecholamines are Neurotransmitters derived from amino acid Tyrosine. It has been recently, (Debanjan et al., 2009) established that Catecholamines (RAO et al., 2007; Taylor et al., 2000; Taylor et al., 2005) are of recent interest in regulation of angiogenesis. Elevated chromogranin A (CgA) level is linked to Catecholamine, the effect of which is lifelong. Cancer cells behave like leaky dielectrics exhibiting the Characteristic Capacitance Relaxation (CR) Phenomenon (Basak et al., 2005; 2008 and 2009; Basak and Ghosh, 2006) [U.S Patent No.5691178, 1997 of T.K.Basak].

Chromaffin cells of the adrenal medulla contain chromogranin A (CGA) which is co-stored and co-released with Catecholamines (Epinephrine Norepinephrine) from storage granules in the adrenal medulla, it plays a catalytic role in granule biogenesis (Mosley et al. 2007). The nucleotide sequence showed that human CGA is a 439 amino acid protein preceded by an 18-residue signal peptide.

It was found (Wu et al., 1991) that the CGA gene has 8 exons and 7 introns spanning about 11kb. CGA is a member of granins, which are a family of acid proteins present in the secretory granules of a wide variety of endocrine and neuroendocrine cells with numerous pairs of basic amino acids as potential cleavage sites. Granins seem to be the precursors of biologically active peptides, which may act as helper proteins in the packaging of peptide hormones and neuropeptides. Biological function of CGA was investigated using CGA-null mice (Mahapatra et al., 2005). It was found in these animals: a decrease in chromaffin granule size and number, increase in blood pressure, loss of diurnal blood pressure variation, increase in left ventricular mass and cavity dimensions, decrease in adrenal catecholamine and neuropeptide Y contents, and an increase in plasma catecholamine and neuropeptide Y concentrations. It can be stated that CGA has a definitive role in the autonomic control of circulation. CGA was found to be an on/off switch, which is sufficient by itself to drive dense-core secretory granule biogenesis and hormone sequestration in endocrine cells (Kim et al., 2001).

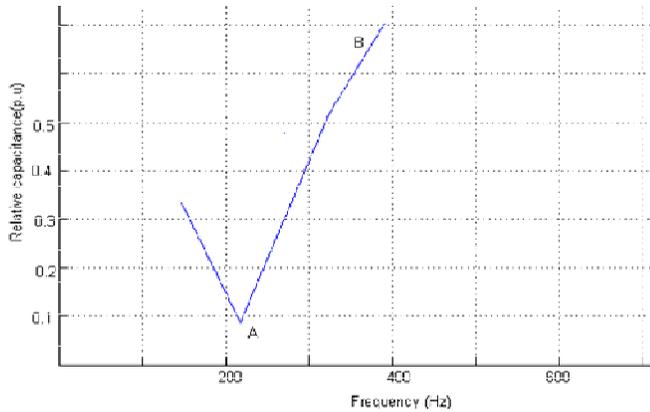


Figure 1. Capacitance Relaxation Curve Of Cancer Cells

Cga is a precursor of biologically active peptides, which act as autocrine or paracrine negative modulators of the neuroendocrine system. To these peptides belong vasostatin 1 with antiadrenergic effects (Gallo et al., 2007), which is a strong inhibitor of glucose induced insulin release from the pancreas, parastatin inhibiting low Ca²⁺ -stimulated parathyroid secretion (Fasciotta et al., 1993), and catestatin, which is a catecholamine released -inhibitory peptide (Rao et al., 2007, Taylor et al., 2000). CGA is secreted by a great variety of peptide-producing endocrine neoplasms such as pheochromocytoma, parathyroid adenoma, medullary thyroid carcinoma, carcinoids, oat-cell lung cancer, pancreatic islet-cell tumors, and aortic-body tumor. In this respect the clinical usefulness of CgA as a neuroendocrine serum marker is well established.

An additional important finding is the existence of the statistically significant difference of CgA expression between benign and malignant pheochromocytomas (Feng et al., 2005, Portela-Gomes et al., 2004). Plasma CgA is progressively higher in malignant pheochromocytoma markedly elevated chromogranin.

It is to be noted that the repeated measurement of circulating CGA over a period of months following removal of a tumor is a good indicator of remission or relapse of the disease. The increased concentrations of circulating CgA were found not only in pheochromocytoma but also in other species of neuroendocrine tumors. It is important to note the finding that in addition to plasma calcitonin, carcinoembryonic antigen and CgA could differentiate between stable and progressive MTC, and both are most useful markers in the follow-up of MTC.

METHODOLOGY

The extracts of tumor cells (1 mg) was cleaned by distilled water and dissolved with lipoproteins in 15ml acetone and kept in the laboratory at room temperature (about 25°C) during the phase of

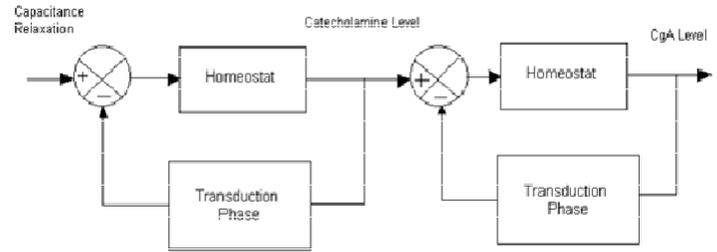


Figure 2. Block Diagram Representation of the model

the experiment. The system developed (Gliozzi and Basak 1986) and described here uses the technique of passing a constant low voltage (100 mv) through the electrodes (Ag-AgCl) dipped in it. At around 200 Hz (Alpha Dispersion region), the capacitance value jumps rapidly in cancer cells the lipoproteins extract separated by a small distance. The data were recorded during measurements with the help of a programmable HP 428A Precision LCR Meter. The measurement cells consisted of glass vessels and the electrodes immersed in it. This measuring technique is developed by the author. The capacitance relaxation phenomena is shown in the figure (1). The observed capacitance relaxation phenomena [U.S Patent No. 5691178, 1997 of T.K. Basak]

Modeling and Simulation

The tool used here is MATLAB for correlation of CgA with capacitance relaxation phenomenon with catecholamine. The MATLAB simulation Block Diagram in this respect is shown below Figure 2.

Homeostat is a controller which maintains static or dynamic conditions in the internal environment of a subject. Transduction phase is a characteristic of a subject which controls physiological parameters along with homeostat (Basak et al., 2005).

Here the transfer function of catecholamine homeostat is taken as

$$G_1(S) = \frac{1}{S + 1} \text{ and transfer function of corresponding transduction}$$

phase is taken as $H_1(S) = \frac{1}{S^2 + 0.4S + 1}$ and transfer function of modified catecholamine homeostat will be

$$T_1(S) = \frac{G_1(S)}{1 + G_1(S)H_1(S)} = \frac{1}{S^3 + 1.4S^2 + 1.4S + 1} = \frac{1}{S^4 + 2.4S^3 + 2.8S^2 + 3.4S + 2}$$

The outputs of modified catecholamine homeostat are shown below:

The transfer function of CgA homeostat is taken as $G_2(S) = \frac{1}{S^2 + S + 1}$ and transfer function of corresponding transduction

phase is taken as $H_2(S) = \frac{1}{S + 0.3}$ and transfer function of

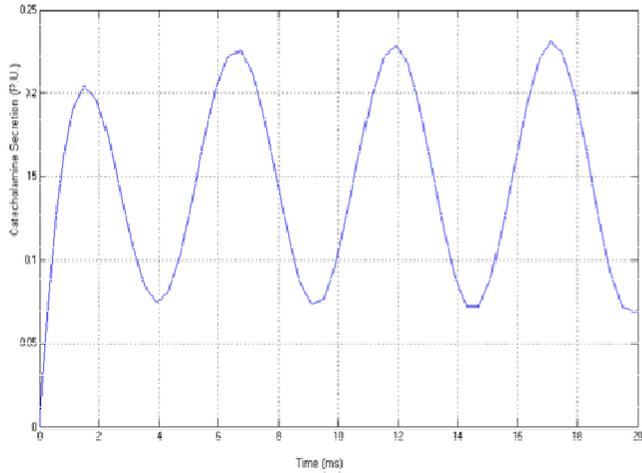


Figure 3. Catecholamine Secretion due to increment of Capacitance Relaxation from 0.1 p.u to 0.3 p.u

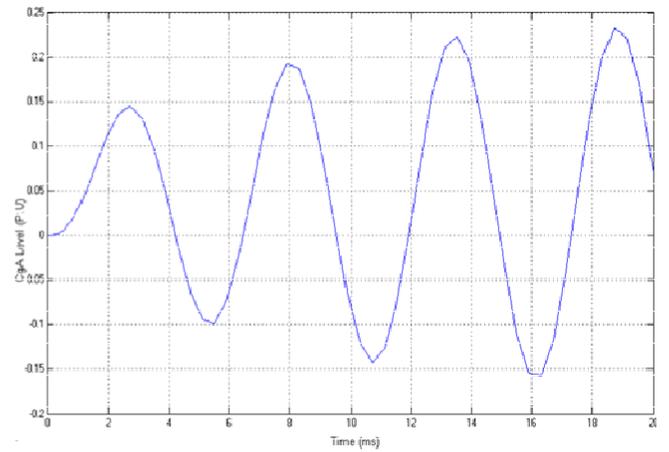


Figure 6. CgA level due to increment of Capacitance Relaxation from 0.1 p.u to 0.3 p.u

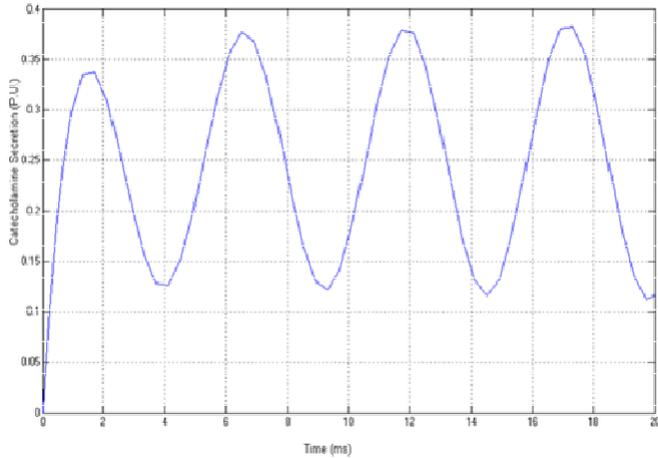


Figure 4. Catecholamine Secretion due to increment of Capacitance Relaxation from 0.3 p.u to 0.5 p.u

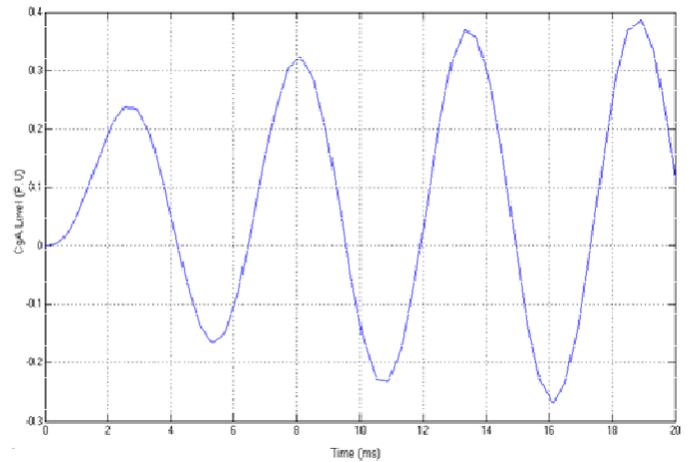


Figure 7. CgA level due to increment of Capacitance Relaxation from 0.3 p.u to 0.5 p.u

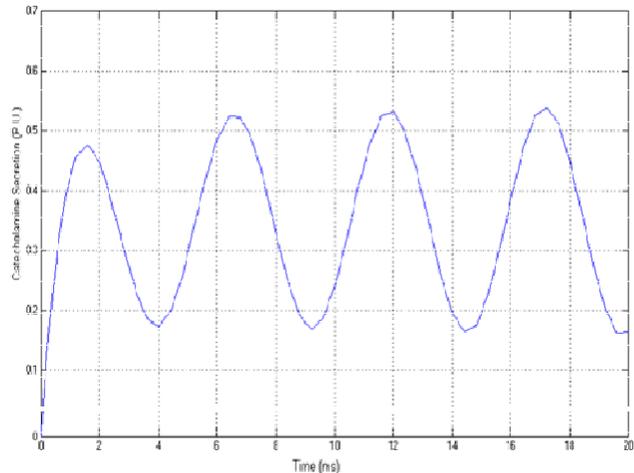


Figure 5. Catecholamine Secretion due to increment of Capacitance Relaxation from 0.5 p.u to 0.7 p.u

modified CgA homeostat will be $T_2(S) = \frac{G_2(S)}{1 + G_2(S)H_2(S)}$

$$= \frac{S^3 + 1.3S^2 + 1.3S + 1}{S^5 + 2.3S^4 + 3.6S^3 + 3.9S^2 + 2.6S + 1.3}$$

The outputs of modified CgA homeostat are shown below (Figures 3,4,5,6,7 and 8)

From the above figures we have calculated the mean values of catecholamine secretion and CgA level due to capacitance relaxation input. The graph reflecting the relation between mean values of catecholamine secretion and CgA level is shown below (figures 9 and 10).

Results

From the results it is interesting to know that the catecholamine and CgA level is linked with the

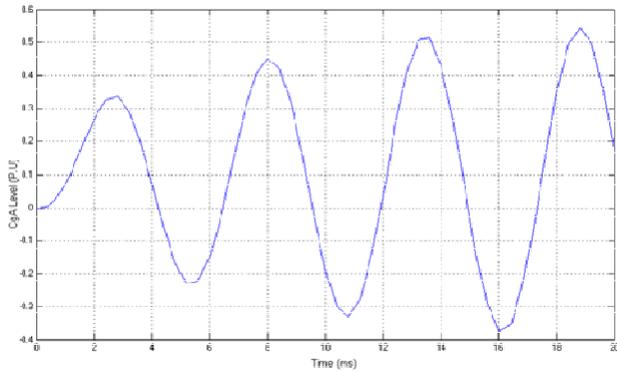


Figure 8. CgA level due to increment of Capacitance Relaxation from 0.5 p.u to 0.7 p.u

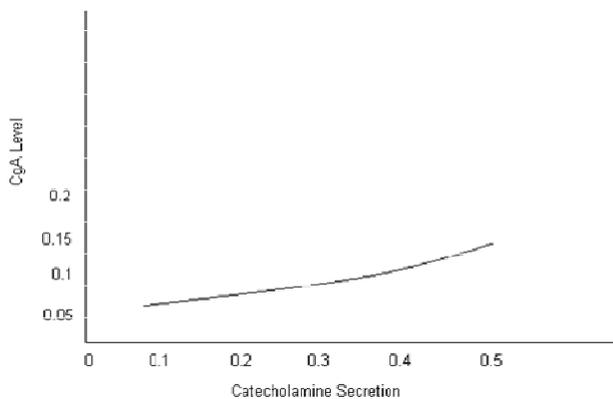


Figure 9. CgA Level Vs Catecholamine Secretion

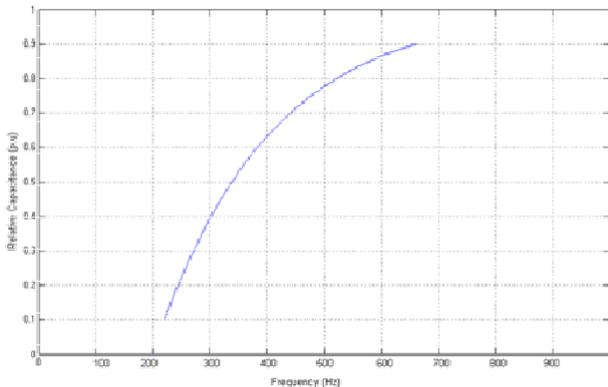


Figure 10. Capacitance relaxation input from 0.1 p.u to 0.9 p.u

capacitance relaxation phenomenon in a novel way. It has been earlier established by A. Moftaquir et al in 1995 in respect of change of CgA against non-epinephrine (NE). Different stages have been derived from figure 10.

DISCUSSIONS AND CONCLUSIONS

The progressive rise in CgA levels has been correlated in different stages with the Capacitance relaxation

phenomenon. The initial stage correlation corresponds to Capacitance relaxation from 0.1pu to 0.5 pu, the second stage correlation corresponds to Capacitance relaxation from 0.1pu to 0.7 pu, and the last stage correlation corresponds to Capacitance relaxation from 0.1pu to 0.9 pu. The mean value of CgA corresponding to different stages was derived from the output of the catecholamine linked to capacitance relaxation phenomenon. The mean value of CgA against catecholamine is shown in Figure 9. It is interesting to note that the mean value of CgA level derived from MATLAB simulation progressively raises with progression of tumor angiogenesis. This fact is established here in a novel way with capacitance relaxation phenomenon linked to catecholamine.

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