A Model Of The Human Stress Response In Relation To The Gastrointestinal Tract

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Introduction

Alterations in gastrointestinal (GI) motor functions and acid secretions of the stomach in humans as a result of stress are substantial enough to warrant further observation. In our modeling of this mechanism, we restricted our attention to fluxes in GI acid secretion rates with respect to their contribution to ulceration of the stomach wall. Following a period of intensive research on relevant background information on the topic, we were able to establish a simple system of differential equations to analyze and evaluate the tendencies and mechanics of this complex biological system. We then simplified our system drastically, so as to focus specifically on two hormones, corticotropin-releasing hormone (CRH) and glucocorticoids (GC), that are particularly useful for analysis of the human stress response in general. Analysis of the interaction of these two hormones provide a rudimentary picture from which we may speculate on the nature of the generalized human stress response and its respective implications.

Central Components Of The Stress Response

Stress is defined as an acute threat to the homeostasis of an organism by real (physical) or perceived (psychological) events [1]. In humans, the stress response is regulated by the autonomic nervous system. The sympathetic nervous system (SNS) is activated by a stressor, whether external or internal, and activates the body's general stress response. The parasympathetic nervous system (PNS) compliments the effects of the SNS and restores the body back to homeostasis, following the conclusion of the stress period [2]. More specifically, during the stress period, the SNS inhibits digestion, diminishes appetite, constricts blood flow, decreases allocation of metabolic energy to growth, reproductive functions, increases the secretion of neurotransmitters, etc. The PNS, in turn, restores all of these actions to their normal levels of function– that is, prior to/in the absence of stress.

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The HPA axis-response is vital to the generalized stress response in the human body and is most relevant to our model. Any general stressor stimulates the secretion of CRH by the paraventricular nucleus (PVN) of the hypothalamus. CRH, in turn, stimulates the secretion of adrenocorticotrophic hormone from the pituitary gland, which then stimulates the secretion of GC from the adrenal gland [3].

The regulation of this system depends on the concentration of GC in the body. Once GC levels have reached a certain setpoint, which varies more or less at any given time, the PVN ceases to secrete CRH. Thus, there is much individual variation in terms of the sustainable length of the body's stress response. Hence, this negative-feedback loop between CRH and GC not only returns the concentration of these two hormones to very low levels under normal conditions, so as to maintain homeostasis, but prevents a potentially detrimental stress response by the body.

Effects Of Stress On Gastrointestinal Function

Homeostasis in the stomach lumen is established by a balance between the secretion of hydrochloric acid (HCl), the formation of a protective layer of mucin along the stomach wall, and the rate of gastric intake and pyloric emptying at any given period of time [4]. Oxyntic glands, which are situated amongst the epithelium cells that compose the stomach wall, contain both parietal cells, which secrete HCl, and mucus neck cells, which secrete mucus and Bicarbonate (HCO_3^-). HCO_3^-, which is secreted in mucus, reacts with hydroxyl ions from HCl to form water and carbon dioxide. The interaction of HCl and unbound mucus forms the protective mucus layer along the epithelium of the stomach.

The neurotransmitter Acetylcholine (ACh), which is secreted by pre-and post-ganglionic parasympathetic neurons, increases HCl, HCO_3^-, and mucus secretion rates by binding to their respective release sites [5]. During a period of stress, CRH diminishes the secretion rates of these chemicals by binding to their respective release sites. Current research indicates that ACh levels remain stable nonetheless, though the implications of this conclusion are irrelevant to our model.

Model Description: Preliminary Results

Our initial, simple model for analysis of this stress response system with

respect to the stomach expressed the risk of ulceration of the stomach wall in terms of [CRH] and [GC] at any given time. That is:

$$X(t) = e^{-k_1 t} \int_0^t e^{k_1 s} \, f(s) \, ds$$

$$Y(t) = G_x e^{-k_2 t} \int_0^t e^{-(k_1 - k_2)s} \, ds \int_0^T e^{k_1 T} \, f(T) \, dT$$

$$U(t) = \int_0^t K_4 Y(s) - K_3 X(s) \, ds$$

as derived from the following set of linear differential equations:

$$\frac{dX}{dt} = f(t) - K_1 X + K_5 U \qquad\qquad X(0) = 0$$

$$\frac{dY}{dt} = G_x X - K_2 Y \qquad\qquad Y(0) = 0$$

$$\frac{dU}{dt} = K_4 Y - K_3 X \qquad\qquad U(0) = C,$$
$$\text{for } C \geq 0$$

<div align="center">(see Glossary for an explanation of the coefficients)</div>

While this system of equations was constructed without the incorporation of the negative−feedback loop between CRH and GC, it gave us a mathematical means to begin actually analyzing the behavior of this system. Research shows that damage from stress results after the conclusion of the stress period, at which point the human body contains a much higher [GC] than normal. While there currently seems to be no solid consensus concerning the question of whether or not excess glucocorticoids directly harm the body or not, this model avoids making either assumption and in turn proved helpful.
Note that, in the absence of stress, [CRH] and [GC] are essentially zero. The amount/risk of ulceration prior to a period of stress in an individual, however, is much more variable and can be expressed as some constant, ie.

U(t)= C, with C dependent on X, Y, and other external factors that are too complex for our simple analysis here (ex. genetics, lifestyle, etc.).

   In our basic model, we noted that, as expected, for any function, f (t), that is the mathematical representation for the effect of stress on the body, any changes in [CRH] has a direct effect on [GC]. If we take f (t) as some constant, for example, we obtain results similar to Fig. 1, for the X−Y system, respectively:

Figure 1
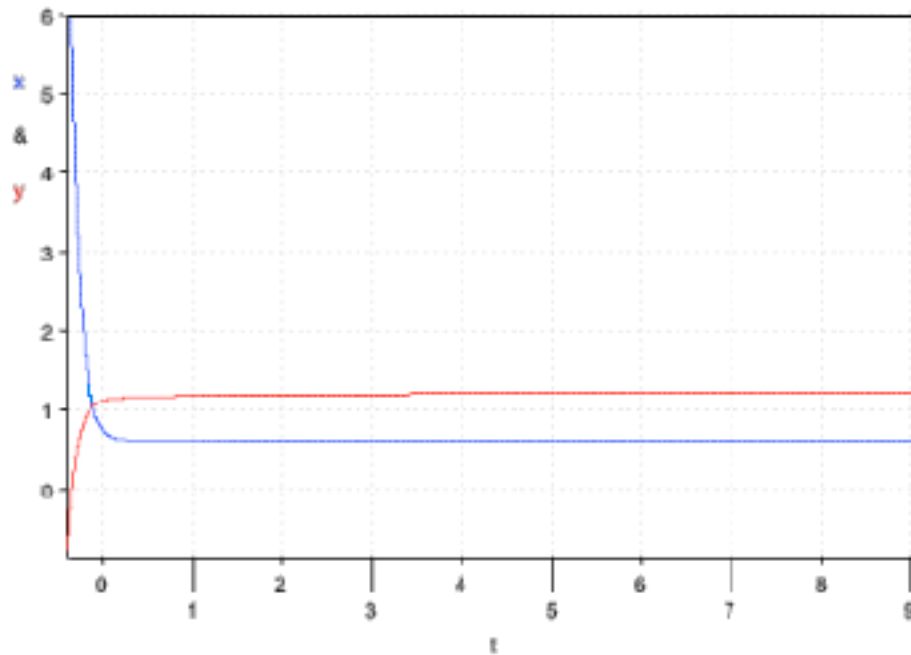
   Clinical results show that, during stress, [CRH] and [GC] will both increase to some maximum concentration and thereafter decline to essentially zero once again, irregardless of the nature of the stressor. The secretion/decay rates of CRH, however, are substantially greater than that of GC− that is, by the end of the stress period, [CRH] will already be approximately equal to zero, while [GC] will have just reached its peak value. As was expected, our initial X−Y system does not model this behavior very well. Hence we proceed to improve this part of the model before applying it to the risk/amount of ulceration function U(t).

## Refinement/Analysis Of The Model

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Upon further research, we learned of the negative−feedback loop between CRH and GC and set forth to incorporate this into our model. Focusing on the [CRH]−[GC] system of interaction, we produced the following autonomous system of differential equations:

$$\frac{dX}{dt} = f(t) - K_1 X - K_3 XY \qquad\qquad X(0) = 0$$

$$\frac{dY}{dt} = G_x X - K_2 Y - K_3 XY \qquad\qquad Y(0) = 0$$

After analyzing this system and its respective eigenvalues/eigenvectors, we expected two types of equilibrium points. Specifically, a stable nodal sink in the first X−Y quadrant and an unstable saddle point in the third X−Y quadrant. Since only positive values of X and Y are of applicable use, we restrict our attention to the stable equilibrium point. For stress functions f (t) close to zero, we expect equilibrium near the example point in Fig. 2 (highlighted in red in the phase portrait):
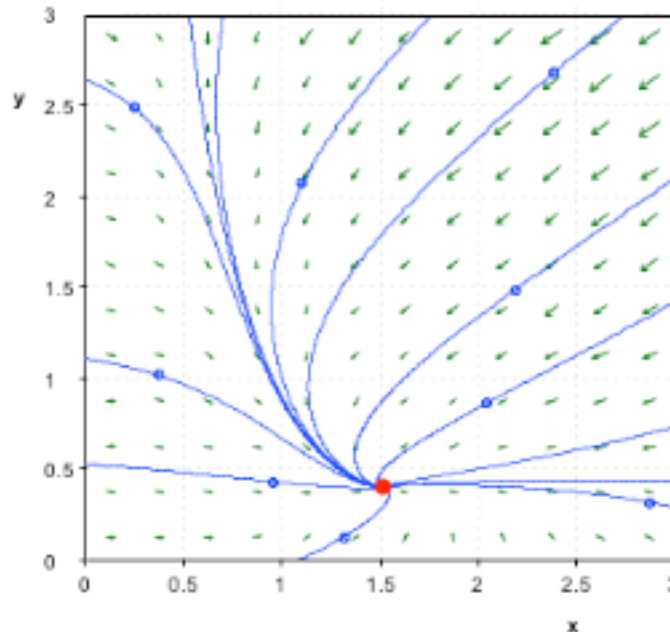
Figure 2
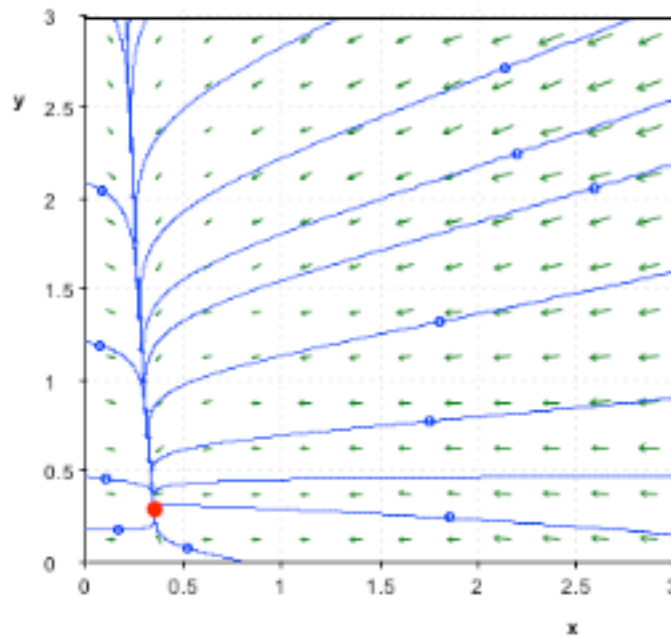
thus confirming our expectations.

     Notice, however, that if we increase f (t) without proportionately increasing the values of the various parameters of our X−Y system, this behavior changes, as such:

Figure 3

     As illustrated by the above graph, while we still expect the system to reach a stable equilibrium, the point shifts from a nodal sink to a spiral sink.

     Due to this curiosity, we decided to focus specifically on this X−Y system. That is, we assumed some constant output effect on the thickness of the mucin wall in the stomach lumen resulting from the stress response. This, in turn, reflects on the risk/amount of expected ulceration that will occur. Such, we assume that the mucin wall maintains some constant thickness continuously, dependent on the behavior of this X−Y system.

     To further analyze this X−Y system, we used non−dimensional analysis and the Buckingham π theorem to re−express our system in non−dimensional terms, reducing the number of parameters in our DE equations to 3. We thus produced the following system:

$$\frac{d\overline{X}}{dt} = A(1 - \overline{X}) - B\overline{X}\,\overline{Y} \qquad\qquad \overline{X}(0) = 0$$

$$\frac{d\overline{Y}}{dt} = C(\overline{X} - \overline{X}\overline{Y}) - \overline{Y} \qquad\qquad \overline{Y}(0) = 0$$

in the case where:

$$A = \frac{K_1}{K_2} \qquad B = \frac{G_x}{K_2} \qquad C = \frac{f(t)\,K_3}{K_1 K_2}$$

We choose to focus on the set of points at which the stable equilibrium point for the autonomous system changed a node to a spiral sink. As such, after computing the Jacobian matrix for this nonlinear system, we solved for eigenvalue solutions to the characteristic polynomial of this linear approximation. Specifically, we focused on the case in which the discriminant of the quadratic solution to our system's eigenvalues equaled zero– that is, the point at which the equilibrium changes. So, we can consider the discriminant as a function, such that:
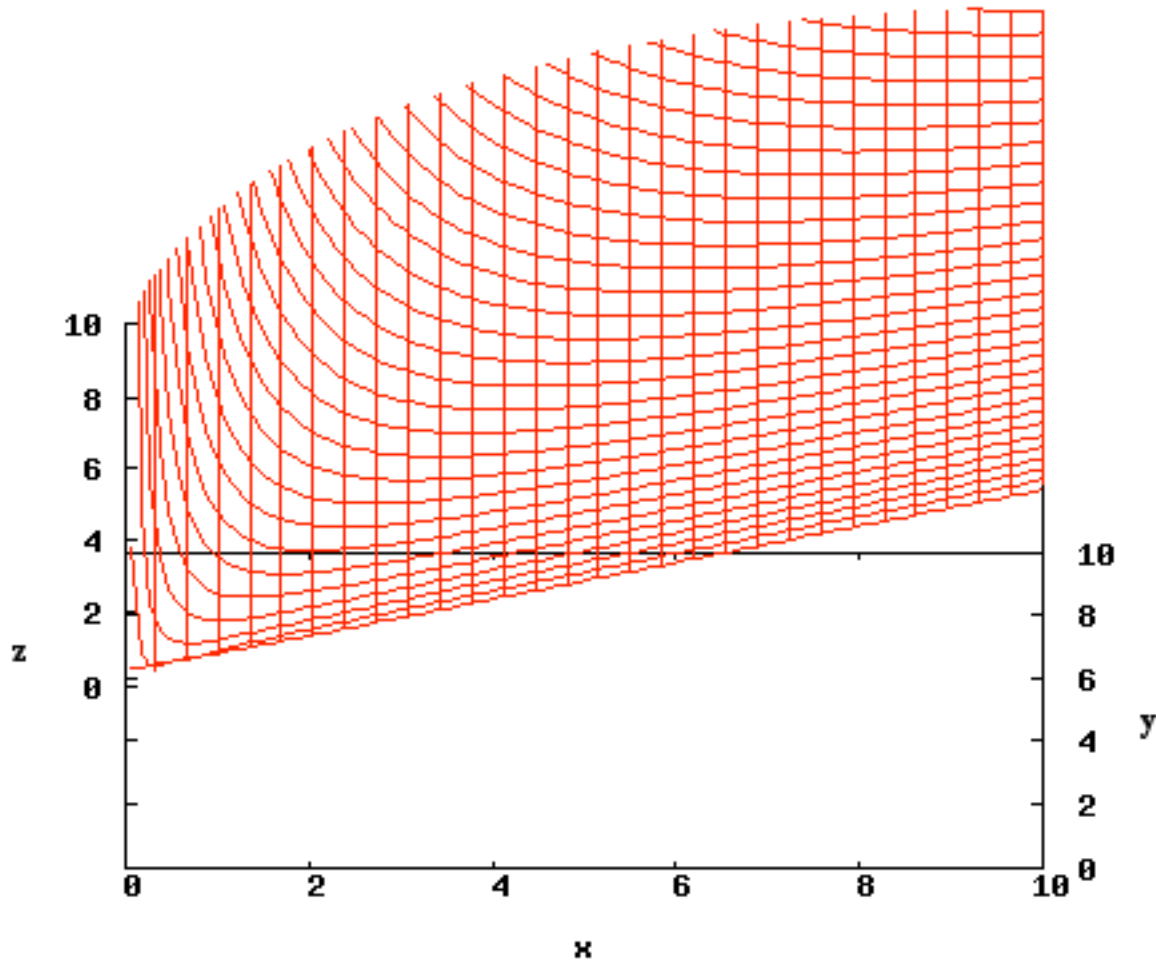
$$F(A,B,C) = \frac{2C^2(B - A)}{C + 1} + (C - A)^2 + \frac{C^2}{(C + 1)^2} = 0$$

I set A=X, B=Y, and C=Z so as to represent this function as a 3–dimensional surface, s.t. G(A,B) = C, with G(A,B) a new function expressing C in terms of A and B. That is:

$$F(X, Y) = \frac{(X + 1)(X - Y)}{2X} - \frac{X^2}{(X + 1)^3} + Y$$

The graph of this function is as follows:

Figure 4

Recall, from before, that we set A=X, B=Y, C=Z. As we observe in the above graph, while X and Y increase proportionately to one another, Z, with respect to X and Y, does not. Since the secretion/decay rate constants of CRH and GC are increasing proportionately to each other, respectively, either the stress input function or the proportion constant of the X−Y negative feedback loop exhibits a change in its proportion to the other parameters of our model. Since the secretion/decay rates of CRH and GC are reflective of the magnitude of the stress input, it seems more logical to conclude that the latter is the case.

CONCLUSIONS

Clinical results show not only that the magnitude of the stress response is proportionate to the stressor. Hence, a more stressful event, a greater

response. In terms of our model, that is, we expect greater secretion/decay/proportion constant values for larger amounts of stress input. Otherwise, the length of the stress response could easily be prolonged past sustainable levels. Such a biological system would be highly unsustainable.

Fig. 4, however, indicates that the magnitude of the X−Y negative feedback loop is increasing at a faster rate that the rest of the system. That is, the body appears to exhibit a mechanism for shortening the period of the stress response with respect to greater, more harmful stresses. This would seem to indicate that the body appears to have evolved a means to decrease the damage it suffers as a result of greater amounts of stress.

Naturally, this model can be greatly expanded upon and improved, given the number of biological variables we either ignored or did not give consideration to. Even so, the basic results we have reached here have several implications for the nature by which the human stress response system evolved and developed.

GLOSSARY

$f(t)$ — stress input function

K_1 — CRH decay rate constant

K_2 — GC decay rate constant

K_3 — proportion constant for the negative effect of CRH on ulceration (NOTE: In our final model, this term is the proportion constant of the X-Y negative feedback loop)

K_4 — proportion constant for the positive effect of GC on ulceration

K_5 — proportion constant for the expression of the amount of ulceration in terms of stress. We choose to express the relationship between X, Y, and U, in our initial model as that of a positive-feedback loop

G_x — growth proportion constant of the positive effect of CRH on the secretion rate of GC

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