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CONTENT

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ULTRADIAN OSCILLATIONS OF CORTICOTROPIN-RELEASING HORMONE (CRH) AND ARGININE VASOPRESSIN (AVP) IN MODELLING OF HYPOTHALAMIC-PITUITARY-ADRENAL AXIS: INFLUENCE OF FEEDBACK LOOP BETWEEN CRH AND CORTISOL

A. S. Stojiljković[1], Ž. Čupić[2], S. Maćešić[3], A. Ivanović-Šašić[2] and Lj. Kolar-Anić[2,3]

[1] Institute of General and Physical Chemistry, University of Belgrade, Studentski trg 12/V, P.O. Box 45, Belgrade, Serbia (alek.stoj@gmail.com)
[2] University of Belgrade, Institute of Chemistry, Technology and Metallurgy, National Institute of Republic of Serbia, Njegoševa 12, 11000 Belgrade, Serbia
[3] Faculty of Physical Chemistry, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia

ABSTRACT
The previously proposed stoichiometric model of the Hypothalamic-Pituitary-Adrenal (HPA) axis activity that took into account arginine vasopressin (AVP), has been further developed to emulate ultradian oscillations of corticotropin-releasing hormone (CRH) and AVP. With this aim, additional coupling of HPA consisting hormones was introduced into this model by reaction between CRH and cortisol (CORT). How additional coupling of hormones affects HPA axis ultradian dynamics and reflects on ultradian oscillations of AVP and CRH concentrations was examined by using numerical simulations and bifurcation analysis. Results show that the rate constant of newly incorporated reaction alone is sufficient to be adjusted only for CRH to exhibit oscillations with optimally prominent amplitudes. Also, oscillation frequencies of CRH were found to be in accordance with findings in the literature under all investigated conditions.

INTRODUCTION
The hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine system involved in maintaining various basal bodily functions and launching life-sustaining adaptive response to internal/external and acute/chronic stressors. This highly complex nonlinear system exhibits a distinctive oscillatory dynamics reflected in ultradian (pulsatile) oscillations superimposed on circadian oscillations of its comprising hormones that are intertwined *via* positive and negative feedback loops [1].

The aim of this study is to simulate ultradian oscillations of both corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) in the previously proposed stoichiometric model of the HPA axis activity in humans that already included both of them [2]. The effect of inducing ultradian oscillations of these species on HPA axis ultradian dynamics was also examined. For these purposes, modelling of reaction mechanism, numerical simulations and bifurcation analysis are used.

MODEL AND METHODS
Stoichiometric model of HPA axis activity in humans, derived from our preceding models [3-7], has been developed to investigate the effects of cholesterol, as the primary precursor of all steroid hormones, on the ultradian and circadian HPA axis activity [8]. This postulated model is then used as the basis to incorporate AVP effects on adrenocorticotropic hormone (ACTH) secretion by reaction steps (R1) - (R5) (Table 1) [2]. As in our previous cases [9-11], we have here additionally coupled the HPA axis hormones by the reaction step (R6) (Table 1). This resulted in the appearance of ultradian concentration oscillations of CRH and AVP. Anyhow,

the extended variant presented here, retained the same number of dynamic variables as in [2]: CRH, AVP, ACTH, cortisol (CORT), aldosterone (ALDO) and cholesterol (CHOL).

Table 1. Summarized reaction steps associated with arginine vasopressin (AVP) in previously proposed stoichiometric network model of HPA axis activity [2] and reaction step incorporated into this model to induce CRH and AVP ultradian oscillations by additionally coupling of the HPA hormones (colored in red).

$\xrightarrow{k_1}$ AVP	(R1)
$\xrightarrow{k_2}$ AVP	(R2)
AVP $\xrightarrow{k_3}$ ACTH	(R3)
CRH + AVP $\xrightarrow{k_4}$ ACTH	(R4)
AVP $\xrightarrow{k_5}$ P_3	(R5)
CRH + CORT $\xrightarrow{k_6}$ P_7	(R6)

All reaction steps presented in Table 1 depict end-results of series of complex biochemical processes. Processes resulting in appropriate inflows of AVP from two different sources, ACTH secretion stimulated by AVP alone and in synergy with CRH, as well as, AVP outflow from HPA system are presented by reaction steps (R1) - (R5) and described in more detail in [2]. Additional coupling of HPA hormones is introduced by reaction between CRH and CORT (R6). In order to examine the effect of additionally coupling the hormones on HPA axis ultradian dynamics, bifurcation analysis based on numerical simulations of dynamic states obtained for different values of rate constant k_6 ((R6), Table 1) was applied. Numerical simulations were conducted using the Matlab software package and the ode15s solver routine based on the Gear algorithm for integration of stiff differential equations. In all simulations, rate constants of reaction steps related to the inflows of AVP ((R1) in Table 1) [2] and CRH ($\rightarrow$CRH) [2, 8] into the pituitary portal system from the same parvocellular neuronal population of the hypothalamic paraventricular nucleus, were kept the same and equal to 1.83×10^{-8} mol dm^{-3} min^{-1} as in [2]. Also, the rate constant of their synergistic reaction, depicted by reaction step (R4) in Table 1, in this study had value of $k_4 = 3.66 \times 10^2$ mol^{-1} dm^3 min^{-1}. The values of other rate constants in this HPA axis model were the same as in [2], unless otherwise specified. Also, in all simulations, the absolute and relative tolerance errors were 3×10^{-20} and 1×10^{-14}, respectively. The initial concentrations, expressed in mol dm^{-3} and marked as M, were: $[CHOL]_0 = 3.4 \times 10^{-4}$ M, $[CRH]_0 = 1 \times 10^{-12}$ M, $[AVP]_0 = 1 \times 10^{-12}$ M, $[ACTH]_0 = 8 \times 10^{-8}$ M, $[CORT]_0 = 4 \times 10^{-8}$ M and $[ALDO]_0 = 1.5 \times 10^{-9}$ M.

RESULTS AND DISCUSSION

Results presented in Figure 1 show that the rate constant of HPA hormones additional coupling (k_6) can influence the amplitude of cortisol oscillations and dynamical regime changes of the HPA system. Namely, for values of $k_6 < 10^7$ M^{-1} min^{-1}, the influence of k_6 is very low to non-existent and the HPA system exhibits oscillatory dynamics. By increasing the value of k_6 (for $k_6 > 10^7$ M^{-1} min^{-1}), the system transits from oscillatory dynamic states to stable steady states through supercritical Andronov-Hopf (AH) bifurcation. Additionally, by increasing value of k_6, amplitudes of cortisol oscillations increase, reaching a maximum and then rapidly decrease in the vicinity of AH bifurcation. The described cortisol amplitude changes with control parameter could also be directly observed in Figure 2 for selected sample values of k_6, assigned by letters (a) and (b) in Figure 1.

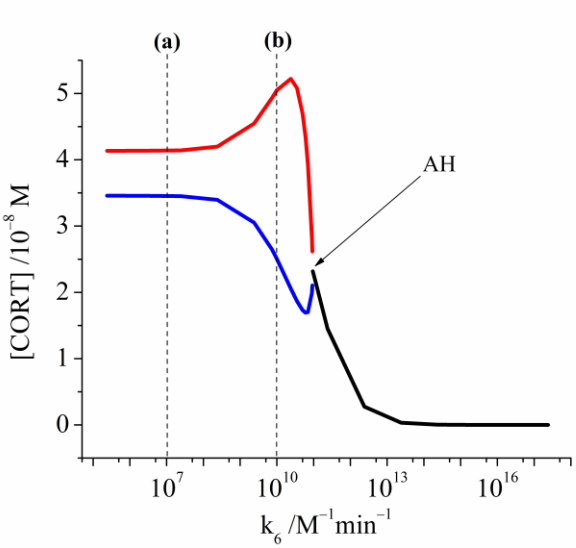

Figure 1. Bifurcation diagram obtained with rate constant k_6 as control parameter. Black curve represent stable steady states. Minimums and maximums in oscillations of cortisol concentrations ([CORT]) are depicted by blue and red curves, respectively. (a) $k_6 = 10^7\ M^{-1}\ min^{-1}$, (b) $k_6 = 10^{10}\ M^{-1}\ min^{-1}$, the value of synergy rate constants was $k_4 = 3.66 \times 10^2\ M^{-1}\ min^{-1}$. All other rate constants used in analysis had values as indicated in [2, 8].

On the other hand, if one considers how different values of the control parameter are reflected on the ultradian oscillations of CRH and AVP, it could be observed that amplitudes of the species oscillation follow a similar pattern of changes with increase in k_6 as cortisol. However, the magnitude of amplitude changes with increase of k_6 differs among two species for a given value of synergy constant. Namely, for $k_6 = 10^7\ M^{-1}\ min^{-1}$, the amplitudes of CRH and AVP are both extremely small as to not exist at all (Figure 2, (a)). On the other hand, when $k_6 = 10^{10}\ M^{-1}\ min^{-1}$ (Figure 2, (b)) is applied, amplitudes of both species increased, but the magnitude of this change is considerably higher in the case of CRH than in the case of AVP for which the amplitude is almost non observant. Further increase of k_6 did not change the amplitude of AVP noticeably. All this indicates that for a given set of rate constants in this HPA axis model, the additional coupling of hormones has dominant effect on CRH ultradian oscillations. On the other hand, if different values of the synergy constant or the rate constant(s) of some other reaction(s) in the model were applied, conditions for AVP to also exhibit ultradian oscillations with optimal amplitudes would be probably found. Furthermore, in all simulations oscillation frequency of CRH was found to range from 2.1 to 2.6 oscillations per hour, which is in accordance with the literature [12]. All these results indicate that feedback loop between CRH and CORT impacts the CRH to exhibit ultradian oscillations.

CONCLUSION

The previously proposed stoichiometric model of HPA axis activity that included AVP is extended to emulate ultradian oscillations of both CRH and AVP. Furthermore, conditions were found in this study only for CRH to exhibit optimally prominent oscillations with frequencies that agree well with experimental findings reported in the literature. Thereby, a step closer is made to veritably emulate properties of the real HPA axis activity by this model.

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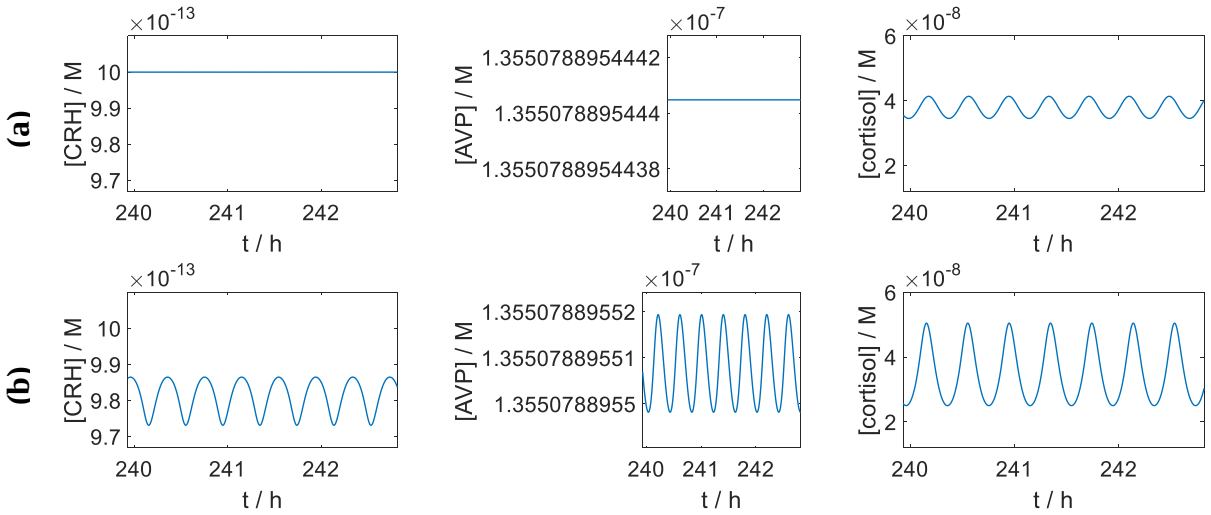

Figure 2. Temporal evolutions of concentrations of CRH, AVP and cortisol ([CRH], [AVP] and [cortisol]) for two selected values of control parameter (k_6) in bifurcation diagram in Figure 1, for the arbitrarily chosen time interval between around 240 and 243 hours. (a) $k_6 = 10^7\ M^{-1}\ min^{-1}$, (b) $k_6 = 10^{10}\ M^{-1}\ min^{-1}$. The value of synergy rate constants was $k_4 = 3.66 \times 10^2\ M^{-1}\ min^{-1}$. All other rate constants used in this study had values as indicated in [2, 8]. **s**Concentrations of all presented species are given in M = mol dm^{-3}.

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