PHYSICAL CHEMISTRY 2021

15th International Conference
on Fundamental and Applied Aspects of
Physical Chemistry

Proceedings
Volume I

The Conference is dedicated to the

30th Anniversary of the founding of the Society of Physical Chemists of Serbia

and

100th Anniversary of Bray-Liebhafsky reaction

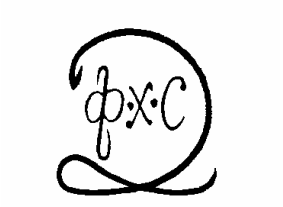
September 20-24, 2021
Belgrade, Serbia

Title: Physical Chemistry 2021 (Proceedings) **ISBN** 978-86-82475-40-8
Volume I: ISBN 978-86-82475-38-5
Editors: Željko Čupić and Slobodan Anić
Published by: Society of Physical Chemists of Serbia, Studentski Trg 12-16, 11158, Belgrade, Serbia
Publisher: Society of Physical Chemists of Serbia
For Publisher: S. Anić, President of Society of Physical Chemists of Serbia
Printed by: ″Jovan″, <Printing and Publishing Company, 200 Copies
Number of pages: 6+344, Format A4, printing finished in December 2021

Text and Layout: ″Jovan″

200 - *Copy printing*

CONTENT



PHYSICAL CHEMISTRY 2021

15th International Conference on
Fundamental and Applied Aspects of
Physical Chemistry

Organized by

The Society of Physical Chemists of
Serbia

in co-operation with

Institute of Catalysis Bulgarian Academy of Sciences

and

Boreskov Institute of Catalysis Siberian Branch of
Russian Academy of Sciences

and

University of Belgrade, Serbia:

Faculty of Physical Chemistry
Institute of Chemistry, Technology and Metallurgy
Vinča Institute of Nuclear Sciences
Faculty of Pharmacy

and

Institute of General and Physical Chemistry, Belgrade, Serbia

International Organizing Committee

Chairman: S. Anić (Serbia)
Vice-chairman: M. Gabrovska (Bulgaria)
A. A. Vedyagin (Russia)
S. N. Blagojević (Serbia)

Members: N. Cvjetićanin (Serbia), S. M. Blagojević (Serbia), M. Daković (Serbia), J. Dimitrić Marković (Serbia), T. Grozdić (Serbia), Lj. Ignjatović (Serbia), D. Jovanović (Serbia), M. Kuzmanović (Serbia), D. Marković (Serbia), B. Milosavljević (USA), M. Mojović (Serbia), N. Pejić (Serbia), M. Petković (Serbia), A. Popović-Bjelić (Serbia), B. Simonović (Serbia), M.Stanković (Serbia), B. Šljukić (Serbia), G. Tasić (Serbia), S. Veličković (Serbia), N. Vukelić (Serbia)

International Scientific Committee

Chairman: Ž. Čupić (Serbia)
Vice-chairman: V. Bukhtiyarov (Russia)
S. Todorova (Bulgaria)
B. Adnađević (Serbia)

Members: S. Anić (Serbia), A. Antić-Jovanović (Serbia), A. Azizoğlu (Turky), R. Cervellati (Italy), G. Ćirić-Marjanović (Serbia), V. Dondur (Serbia), I. I. Grinvald (Russia), R. Jerala (Slovenia), M. Jeremić (Serbia), G. N. Kaluđerović (Germany), E. Kiš (Serbia), A.V. Knyazev (Russia), Lj. Kolar-Anić (Serbia), U. Kortz (Germany), T. Kowalska (Poljska), A. Lemarchand (France), G. Lente (Hungary), Z. Marković (Serbia), S. Mentus (Serbia), K. Novaković (UK), N. Ostrovski (Serbia), V. Parmon (Russia), Z. Petkova Cherkezova-Zheleva (Bulgary), M. Plavšić (Serbia), J. Savović (Serbia), G. Schmitz (Belgium), I. Schreiber (Czech), L. Schreiberova (Czech), D. Stanisavljev (Serbia), N. Stepanov (Russia), M. Stojanović (USA), E. Szabó (Slovakia), Zs. Szakacs (Romania), Z. Šaponjić (Serbia), Á. Tóth (Hungary), M. Trtica (Serbia), V. Vasić (Serbia), D. Veselinović (Serbia), V. Vukojević (Sweden)

Local Executive Committee

Chairman: S. N. Blagojević
Vice-chairman: A. Ivanović-Šašić
N. Jović-Jovičić
A. Stanojević

Members: M. Ajduković, I. N. Bubanja, A. Dobrota, J. Dostanić, D. Dimić, S. Jovanović, Z. Jovanović, D. Lončarević, M. Kragović, J. Krstić, B. Marković, S. Maćešić, J. Maksimović, S. Marinović, D. Milenković, T. Mudrinić, M. Pagnacco, N. Potkonjak, B. Stanković, I. Stefanović, G. Stevanović, A. Stoiljković, M. Vasić

SPONSORS

Ministry of Education, Science and Technological Development of the Republic Serbia
Institute of General and Physical Chemistry, Belgrade
Belgrade Analysis d.o.o.

CIRCADIAN RHYTHM FUNCTION COUPLING TO THE UPGRADED HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS WITH INCORPORATED ARGININE VASOPRESSIN

A. S. Stojiljković [1], A. Stanojević [2], A. Ivanović-Šašić [3], Ž. Čupić [3] 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] *Faculty of Physical Chemistry, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia*
[3] *Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia.*

ABSTRACT
An upgraded model of the Hypothalamic-Pituitary-Adrenal (HPA) axis has been developed that advances our previously proposed low-dimensional HPA model by including the effects of arginine vasopressin (AVP) that is a key modulator of HPA axis function. The upgraded model allows us to emulate AVP effects on HPA axis dynamics individually and in synergy with the corticotropin-releasing hormone (CRH). In this work, we examine how coupling of the circadian function through summarised reaction steps describing CRH and AVP biosynthesis in the same neuronal cell group of the hypothalamic paraventricular nucleus (PVN) affects HPA axis dynamics. Results of numerical simulations show that coupling of the circadian function through both, CRH and AVP summarised biosynthesis reaction steps simultaneously, emulates best the HPA axis dynamics, in line with literature findings.

INTRODUCTION
The hypothalamic-pituitary-adrenal (HPA) axis represents a complex neuroendocrine system that couples the functions of hypothalamus, pituitary and adrenal glands to preserve the organism's homeostasis under physiologically normal and various stressful conditions. For that purpose, a proper oscillatory dynamics of HPA axis comprising hormones, with ultradian oscillations (period of 20 minutes to 2 hours) superimposed on circadian oscillations (period of about 24 hours), is an essential precondition [1].

The aim of this study is to examine the coupling conditions between ultradian and circadian rhythms of the hormones of the upgraded HPA axis model with incorporated arginine vasopressin (AVP), using modelling of reaction mechanism and numerical simulations. For that purpose, a low-dimensional model with five dynamic variables is employed as the initial model [2]. The upgraded low-dimensional model is now consisted of six dynamic variables: the corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), adrenocorticotropic hormone (ACTH), cortisol (CORT), aldosterone (ALDO) and cholesterol (CHOL), as the only precursor of all steroid hormones.

MODEL AND METHODS
The pre-existing low-dimensional HPA model [2] has been extended to describe arginine vasopressin (AVP) effects on adrenocorticotropic hormone (ACTH) release (Table 1).

Table 1. Summarised reaction steps associated with arginine vasopressin (AVP) that are incorporated in the upgraded low-dimensional model of the HPA axis

$\xrightarrow{k_1}$ 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)

All reaction steps presented in Table 1 describe end-results of a series of complex biochemical processes. In more detail, series of processes of the biosynthesis of AVP in the parvicellular part of the hypothalamic paraventricular nucleus (PVN), and in the magnocellular neurosecretory system of the hypothalamus, resulting in corresponding inflows of AVP into the pituitary portal system are described by reaction steps (R1) and (R2), respectively. Reaction step (R3) describes summarised series of complex biochemical processes resulting in ACTH secretion stimulated by AVP originating from both of these neuronal populations. Series of complex biochemical reactions leading to ACTH production and release due to a strong synergistic effect of CRH and AVP on ACTH secretion by the pituitary gland, are summarised by reaction step (R4) [3]. Reaction step (R5) describes summarised series of complex biochemical processes leading to the elimination of AVP.

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, the absolute and relative tolerance errors were $3\cdot10^{-20}$ and $1\cdot10^{-14}$, respectively. The initial concentrations, expressed in mol dm^{-3} and designated as M, were: $[CHOL]_0 = 3{,}4\cdot10^{-4}$ M, $[CRH]_0 = 1\cdot10^{-12}$ M, $[AVP]_0 = 1\cdot10^{-12}$ M, $[ACTH]_0 = 8\cdot10^{-8}$ M, $[CORT]_0 = 4\cdot10^{-8}$ M and $[ALDO]_0 = 1{,}5\cdot10^{-9}$ M. If not otherwise stated, the rate constants were: $k_1 = 1{,}83 \cdot 10^{-8}$ mol dm^{-3} min^{-1}, $k_2 = 1{,}537 \cdot 10^{-9}$ mol dm^{-3} min^{-1}, $k_3 = 7{,}79 \cdot 10^{-3}$ min^{-1}, $k_4 = 1{,}098 \cdot 10^{9}$ mol^{-1} dm^3 min^{-1} and $k_5 = 1{,}386 \cdot 10^{-1}$ min^{-1}. The circadian rhythm function $D=d_1 - 0{,}079145093 \cdot d_2 + \{0{,}064 \cdot \sin(2\pi t/1440) + 0{,}12 \cdot \mathrm{abs}[\sin(\pi t/1440)]\} \cdot d_2$ is used to couple to the upgraded model through the reaction steps describing biosynthesis of CRH and AVP in the same neuron cell groups of the hypothalamic PVN.

RESULTS

Couplings of the circadian function D to the upgraded HPA model through reaction steps related to the inflows of CRH and AVP into the system from the same neuron cell group and sharing the same rate constant = $1{,}830 \cdot 10^{-8}$ mol dm^{-3} min^{-1}, have been examined *in silico* for inflow reaction steps both individually and simultaneously (Figure 1.). These results were further compared with those obtained from the initial HPA model, where CRH is the only species that influence ACTH secretion. The same value for rate constant is used. Namely, when function D is coupled to the upgraded model through CRH and AVP inflow reaction steps simultaneously (Figure 1, case (3)), results show decrease of the amplitude of [CORT] ultradian oscillations compared to those obtained by the coupling of function D through CRH inflow reaction step solely (Figure 1, case (1)). On the other hand, function D coupling through solely AVP inflow reaction step (R1), produces very low amplitude of ultradian oscillations (A_{UD}), that are uniformly superimposed on circadian [CORT] oscillations of also low circadian amplitudes (A_{CD}) (Figure 1, case (2)). By comparing the results obtained by coupling the function D through CRH inflow to the initial minimal HPA model that does not include AVP (Fig. 1, (0)) and the upgraded model with AVP using the same rate constant value for CRH inflow (Fig. 1, (1)), it can be noticed that cortisol A_{UD} is higher in the upgraded HPA model,

which is in better agreement with experimentally measured values reported in the literature. Taken together, A_{UD} increases between the examined cases in the following manner: $A^{(2)}_{UD} < A^{(0)}_{UD} < A^{(3)}_{UD} < A^{(1)}_{UD}$. There are numerous studies on humans indicating several-fold increased [CORT] due to CRH and AVP acting synergistically on corticotrope cells that could fall into the domain of A_{UD} [4-6].

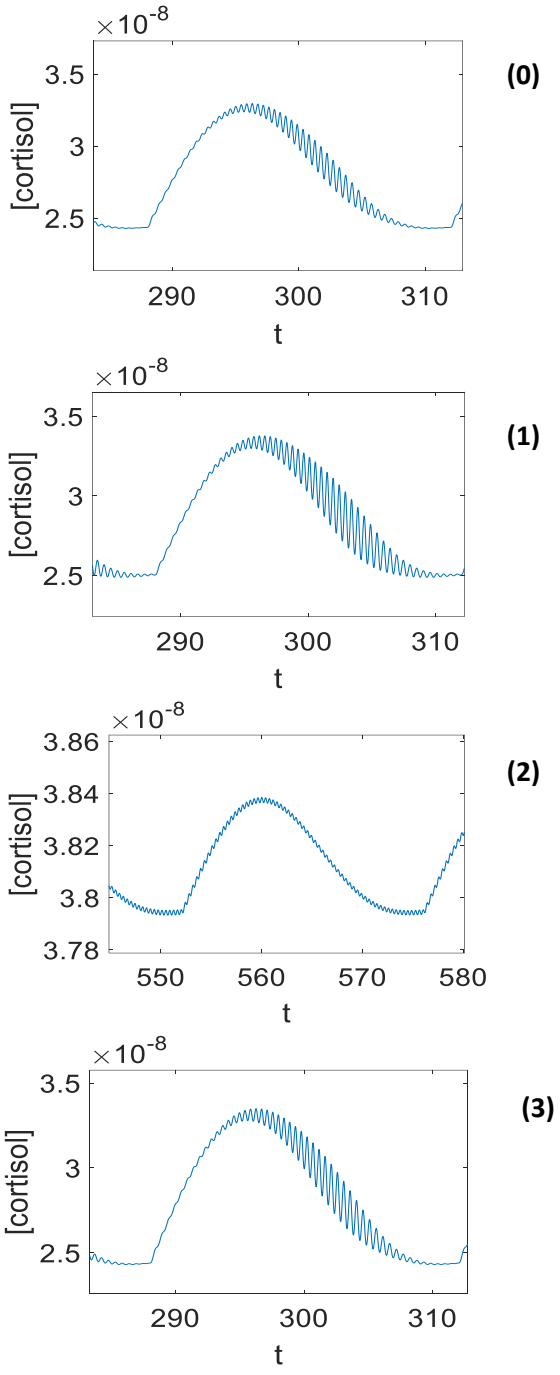


Figure 1. Temporal evolution of cortisol concentration ([CORT]) emulated using the minimal or the upgraded model of HPA axis dynamics with the circadian function being coupled through CRH and/or AVP inflow. Daily changes in blood cortisol concentration emulated using: **(0)** the minimal HPA axis model without AVP, when the rate constant of CRH inflow is $1{,}830 \cdot 10^{-8}$ M; **(1)** the upgraded HPA axis model with AVP, when the rate constant of CRH inflow is $1{,}830 \cdot 10^{-8}$ M and AVP inflow is disregarded; **(2)** the upgraded HPA axis model with AVP, when the rate constant of AVP inflow is $1{,}830 \cdot 10^{-8}$ M and CRH inflow is disregarded; **(3)** the upgraded HPA axis model with AVP, when the rate constant of CRH and AVP inflow are both $1{,}830 \cdot 10^{-8}$ M.

Of note, when function D is coupled to the model simultaneously through these inflow reaction steps (3) or only through CRH inflow reaction step, (1) parameters of the circadian function D were: $d_1 = 0{,}840978$ and $d_2 = 0{,}957$. On the other hand, when function D is coupled through AVP inflow reaction step (R1) solely (2), corresponding parameters were: $d_1 = 1{,}1331072$ and $d_2 = 0{,}957$. In the initial HPA model, (0) with CRH as the only species that influence ACTH secretion, $d_1 = 0{,}88524$ and $d_2 = 0{,}957$ were parameters of function D coupling only through CRH inflow reaction step. Time is given in hours (h) and cortisol concentration in mol dm^{-3}.

Circadian function D coupling through the CRH inflow reaction step only will result in [AVP] minimum appearing around 8 o'clock in the morning (8 h) and [AVP] maximum around midnight (24 h). This is in contrast with [AVP] extreme values appearance when the function D is coupled through CRH and AVP inflow reaction steps simultaneously (data not shown). Since [AVP] reaches

its minimum in the early evening, around 18-20 o'clock, and a maximum around 2-6 o'clock in the morning [7], the best agreement with experimental results could be achieved when the daily function D is coupled to the model through both, CRH and AVP inflows simultaneously. Additionally, it has been pinpointed in the literature that both parvocellular CRH and AVP participate in the generation of a circadian ACTH and CORT rhythm [8]. In line with these experimental findings, results obtained using the upgraded model favour coupling of the circadian function through CRH and AVP inflow reaction steps simultaneously.

CONCLUSION

The pre-existing low-dimensional mathematical model of HPA axis dynamics is extended to include AVP. This enhances the comprehensiveness and physiological plausibility of the model, while preserving its tractability to mathematical analysis and simulation. A step forward is made by finding the appropriate conditions for coupling between ultradian and circadian rhythms of the HPA axis hormones. However, the proposed model still needs further improvements and refinements for examination of AVP and CRH effects and synergistic influence on the HPA axis dynamics.

Acknowledgement

This study was supported by Ministry of Education, Science and Technological Development of the Republic of Serbia (Contracts no. 451-03-9/2021-14/200146, 451-03-9/2021-14/200026 and 451-03-9/2021-14/ 200051).

REFERENCES

[1] C. Tsigos and G. P. Chrousos, *Journal of Psychosomatic Research* (2002) **53**, 865-871.
[2] V. M. Marković, Ž. Čupić, S. Maćešić, A. Stanojević, V. Vukojević and Lj. Kolar-Anić, *Mathematical Medicine and Biology* (2016) **33** (1), 1–28.
[3] F. A. Antoni, *Frontiers in Neuroendocrinology* (1993) **14** (2), 76-122.
[4] R. A. Salata, D. B. Jarrett, J. G. Verbalis, A. G. Robinson, *The Journal of Clinical Investigation* (1988) **81**(3), 766-774.
[5] C. R. DeBold, W. R. Sheldon, G. S. DeCherney, R. V. Jackson, A. N. Alexander, W. Vale, J. Rivier, and D. N. Orth, *The Journal of Clinical Investigation* (1984) **73**(2), 533-538.
[6] J.H. Liu, K. Muse, P. Contreras, D. Gibbs, W. Vale, J. Rivier, S. S. C. Yen, *The Journal of Clinical Endocrinology & Metabolism* (1983) **57** (5), 1087-1089.
[7] ML Forsling, H Montgomery, D Halpin, RJ Windle, DF Treacher, *Experimental Physiology* (1998) **83** (3), 409-418.
[8] George P. Chrousos, *Endocrinology (1998)* **139** (2), 437–40.