



# On rat brain pumps and persistence: Dr. Stylianos Tsakiris as a brain researcher and mentor

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This focused issue of the *Annals of Research Hospitals* is dedicated to Dr. Stylianos Tsakiris: a brain researcher, university teacher and mentor who retired as Associate Professor of Physiology after serving the academic community of the National and Kapodistrian University of Athens for more than 35 years. Dr. Tsakiris has taught physiology to undergraduates in medicine, dentistry and pharmacy, and has worked in a systematic manner on cellular physiology, with emphasis on the mechanisms through which metabolic diseases, oxidative stress, heavy metals and ageing affect the functionality of critical enzymatic parameters of the cell membrane. His published work includes more than 120 articles indexed in PubMed, and several other published works. This issue honours not only his scientific contribution as a cellular physiologist, but also the mentorship that many of us enjoyed and treasure.

Dr. Tsakiris was born in 1950 in Keratsini, Greece. He studied natural sciences at the National and Kapodistrian University of Athens, before fulfilling his military duties during a troublous period for both Greece and Cyprus (1973–1975). In 1976 he gained a scholarship that allowed him to undertake doctoral studies at the Nuclear Research Centre “Demokritos” under the supervision of Dr. George Akoyunoglou. His PhD thesis on the dynamic regulation of the photosynthetic membrane of the common bean (*Phaseolus vulgaris*) chloroplasts was successfully defended at the Aristotle University of Thessaloniki in 1982. Later that same year, Dr. Tsakiris was appointed as a Lecturer at the Medical School of the National and Kapodistrian University of Athens, embarking on a 35-year-long journey of research and teaching at the Laboratory of Physiology, where he was

subsequently promoted to Assistant Professor and Associate Professor of Physiology (1996 and 2003, respectively).

As a member of staff in a historical and research-oriented department that is the Laboratory of Physiology (formerly known as “Laboratory of Experimental Physiology”), Dr. Tsakiris developed an interest in cellular physiology and rapidly moved on in establishing his own research projects. In his relatively small lab space that could barely fit four people at the same time, he established an array of neurochemical techniques that would be systematically employed in his fascinating projects. Ageing, neurodevelopment, oxidative stress, exercise, toxic and metabolic encephalopathies, inborn errors of metabolism, would become some of the recurring themes of his research. Of particular importance has been his work on sodium-potassium adenosine triphosphatase ( $\text{Na}^+, \text{K}^+$ -ATPase); a major consumer of adenosine triphosphate (ATP) in the brain that maintains the neuronal membrane potential, regulates neuronal excitability and can alter the uptake and release of major neurotransmitters in response to simple or complex external stimuli. Commonly referred to as “the brain pump”,  $\text{Na}^+, \text{K}^+$ -ATPase is now considered as a key transmembrane enzyme (EC 3.6.3.9, formerly EC 3.6.1.3) for the assessment of brain injury following acute and chronic toxic and metabolic insults; a concept that Dr. Tsakiris began to explore quite early in his career (1,2) by studying the enzyme’s activity—its most informative, sensitive and technically-challenging parameter. He did so along with other neurochemical parameters (such as the activity of acetylcholinesterase; AChE), and by employing translationally-sound *in vitro* conditions aiming to simulate

clinical conditions such as phenylketonuria (3) and galactosaemia (4), as well as by setting up collaborations that would provide him access to brain tissue from animals subjected to experimental interventions of varying complexity (5-10).

Dr. Tsakiris had a prolific collaboration with Dr. Kleopatra Schulpis of the Institute of Child Health (Athens), as well as with members of staff of the Laboratory of Experimental Pharmacology of the Medical School of Athens, such as Dr. Haris Carageorgiou and Professor Charis Liapi. Dr. Schulpis played a key role in defining the *in vitro* conditions employed for the simulation of inborn errors of metabolism on rat synaptosomal membranes (4,11), and she facilitated access to patient blood samples that led to the publication of seminal papers (12,13). Noteworthy are also the projects that Dr. Carageorgiou led on the neurotoxic effects of cadmium (14) and hypothyroidism (15) on the adult rat, both followed up by projects shifting the focus from adulthood to neurodevelopment, for which Dr. Tsakiris collaborated with Professor Liapi (16,17). Moreover, a series of projects designed and led by Professor Liapi on the neurotoxic effects of dietary-induced choline-deprivation in neurodevelopment (18) as well as in the absence (19) and presence of comorbidities such as diabetes (20) in adulthood, resulted in the characterization of several novel *in vivo* disease models in rats.

In parallel to the aforementioned projects, Dr. Tsakiris has worked on the *in vitro* neurotoxic effects of aspartame and its metabolites on the postnatal rat hippocampus (21), on the effects of forced swimming on crucial rat brain enzyme activities (22), as well as on a number of projects focusing on membrane-bound enzymatic modulation in athlete- (23) and patient-derived (12,13,24) erythrocytes. Although interested in the improvement of the teaching of physiology (25) and a driving force behind the elective course of “Physiology of Ageing” offered to undergraduate medical students, Dr. Tsakiris would commonly self-identify solely as a researcher.

His dedication in maintaining high standards in his research practice has not obstructed him from introducing an important number of undergraduate medical students to translational research, and from successfully supervising a significant number of doctoral (PhD) projects. In recent years, this dedication took the form of unwavering persistence when a promotion to full professorship became unlikely and retirement loomed.

A nightmare for procrastinating administrators on

the other end of the line, humble and hard-working, Dr. Stylianos Tsakiris has also been a caring and fair mentor for all of us who were fortunate to work under his supervision. To those of us who systematically volunteered as undergraduate research assistants in his lab, co-authorship on publications was assured, and his analytical, tedious and reliable research practice would make a lasting impression. Dr. Tsakiris has been an attentive and encouraging mentor to his students, making sure that we would not only gain insight into the research performed, but we would also have access to material that would broaden our understanding of the translational reasoning behind the witnessed work.

I write on behalf of all contributors in affirming that his legacy is inspiring, and that this Honorary Issue serves as a token of gratitude for his work and mentorship.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

### References

1. Tsakiris S, Deliconstantinos G. Influence of phosphatidylserine on (Na<sup>+</sup>,K<sup>+</sup>)-stimulated ATPase and acetylcholinesterase activities of dog brain synaptosomal plasma membranes. *Biochem J* 1984;220:301-7.
2. Tsakiris S. Na<sup>+</sup>,K<sup>+</sup>-ATPase and acetylcholinesterase activities: changes in postnatally developing rat brain induced by bilirubin. *Pharmacol Biochem Behav* 1993;45:363-8.

3. Tsakiris S. Effects of L-phenylalanine on acetylcholinesterase and Na<sup>+</sup>,K<sup>+</sup>-ATPase activities in adult and aged rat brain. *Mech Ageing Dev* 2001;122:491-501.
4. Marinou K, Tsakiris S, Tsopanakis C, et al. Suckling rat brain regional distribution of Na<sup>+</sup>,K<sup>+</sup>-ATPase activity in the *in vitro* galactosaemia: the effect of L-cysteine and glutathione. *Metab Brain Dis* 2005;20:45-54.
5. Carageorgiou H, Zarros A, Tsakiris S. Selegiline long-term effects on brain acetylcholinesterase, (Na<sup>+</sup>,K<sup>+</sup>)-ATPase activities, antioxidant status and learning performance of aged rats. *Pharmacol Res* 2003;48:245-51.
6. Zarros A, Theocharis S, Skandali N, et al. Effects of fulminant hepatic encephalopathy on the adult rat brain antioxidant status and the activities of acetylcholinesterase, (Na<sup>+</sup>,K<sup>+</sup>)- and Mg<sup>2+</sup>-ATPase: comparison of the enzymes' response to *in vitro* treatment with ammonia. *Metab Brain Dis* 2008;23:255-64.
7. Zarros A, Liapi C, Galanopoulou P, et al. Effects of adult-onset streptozotocin-induced diabetes on the rat brain antioxidant status and the activities of acetylcholinesterase, (Na<sup>+</sup>,K<sup>+</sup>)- and Mg<sup>2+</sup>-ATPase: modulation by L-cysteine. *Metab Brain Dis* 2009;24:337-48.
8. Bimpis A, Papalois A, Tsakiris S, et al. Modulation of crucial adenosinetriphosphatase activities due to U-74389G administration in a porcine model of intracerebral hemorrhage. *Metab Brain Dis* 2013;28:439-46.
9. Zarros A, Liapi C, Al-Humadi H, et al. Experimentally-induced Wernicke's encephalopathy modifies crucial rat brain parameters: the importance of Na<sup>+</sup>,K<sup>+</sup>-ATPase and a potentially neuroprotective role for antioxidant supplementation. *Metab Brain Dis* 2013;28:387-96.
10. Stolakis V, Liapi C, Zarros A, et al. Exposure to ethanol during neurodevelopment modifies crucial offspring rat brain enzyme activities in a region-specific manner. *Metab Brain Dis* 2015;30:1467-77.
11. Schulpis KH, Kalimeris K, Bakogiannis C, et al. The effect of *in vitro* homocystinuria on the suckling rat hippocampal acetylcholinesterase. *Metab Brain Dis* 2006;21:21-8.
12. Schulpis KH, Michelakakis H, Tsakiris T, et al. The effect of diet on total antioxidant status, erythrocyte membrane Na<sup>+</sup>,K<sup>+</sup>-ATPase and Mg<sup>2+</sup>-ATPase activities in patients with classical galactosaemia. *Clin Nutr* 2005;24:151-7.
13. Schulpis KH, Tjamouranis J, Karikas GA, et al. *In vivo* effects of high phenylalanine blood levels on Na<sup>+</sup>,K<sup>+</sup>-ATPase, Mg<sup>2+</sup>-ATPase activities and biogenic amine concentrations in phenylketonuria. *Clin Biochem* 2002;35:281-5.
14. Carageorgiou H, Tzotzes V, Pantos C, et al. *In vivo* and *in vitro* effects of cadmium on adult rat brain total antioxidant status, acetylcholinesterase, (Na<sup>+</sup>,K<sup>+</sup>)-ATPase and Mg<sup>2+</sup>-ATPase activities: protection by L-cysteine. *Basic Clin Pharmacol Toxicol* 2004;94:112-8.
15. Carageorgiou H, Pantos C, Zarros A, et al. Changes in acetylcholinesterase, Na<sup>+</sup>,K<sup>+</sup>-ATPase, and Mg<sup>2+</sup>-ATPase activities in the frontal cortex and the hippocampus of hyper- and hypothyroid adult rats. *Metabolism* 2007;56:1104-10.
16. Stolakis V, Tsakiris S, Kalafatakis K, et al. Developmental neurotoxicity of cadmium on enzyme activities of crucial offspring rat brain regions. *Biometals* 2013;26:1013-21.
17. Koromilas C, Liapi C, Zarros A, et al. Inhibition of Na<sup>+</sup>,K<sup>+</sup>-ATPase in the hypothalamus, pons and cerebellum of the offspring rat due to experimentally-induced maternal hypothyroidism. *J Matern Fetal Neonatal Med* 2015;28:1438-44.
18. Liapi C, Feskou I, Zarros A, et al. Equilibrated diet restores the effects of early age choline-deficient feeding on rat brain antioxidant status and enzyme activities: the role of homocysteine, L-phenylalanine and L-alanine. *Metab Brain Dis* 2008;23:289-301.
19. Liapi C, Kyriakaki A, Zarros A, et al. Effects of adult-onset choline deprivation on the activities of acetylcholinesterase, (Na<sup>+</sup>,K<sup>+</sup>)- and Mg<sup>2+</sup>-ATPase in crucial rat brain regions. *Food Chem Toxicol* 2009;47:82-5.
20. Liapi C, Kyriakaki A, Zarros A, et al. Choline-deprivation alters crucial brain enzyme activities in a rat model of diabetic encephalopathy. *Metab Brain Dis* 2010;25:269-76.
21. Simintzi I, Schulpis KH, Angelogianni P, et al. L-Cysteine and glutathione restore the reduction of rat hippocampal Na<sup>+</sup>,K<sup>+</sup>-ATPase activity induced by aspartame metabolites. *Toxicology* 2007;237:177-183.
22. Tsakiris T, Angelogianni P, Tesseromatis C, et al. L-Cysteine's effect on modulated rat brain enzymes with forced swimming. *Int J Sport Nutr Exerc Metab* 2009;19:285-97.
23. Parthimos T, Schulpis KH, Angelogianni P, et al. The *in vivo* and *in vitro* effects of L-carnitine supplementation on the erythrocyte membrane acetylcholinesterase, Na<sup>+</sup>,K<sup>+</sup>-ATPase and Mg<sup>2+</sup>-ATPase activities in basketball players. *Clin Chem Lab Med* 2008;46:137-42.
24. Schulpis KH, Vlachos GD, Antsaklis A, et al. Modulated human maternal and premature neonatal erythrocyte

membrane enzyme activities in relation to the mode of delivery: *in vitro* restoration with L-carnitine. Clin Chem Lab Med 2011;49:559-62.

25. Tsakiris S, Zarros A. Medical physiology and experimentation: reconsidering the undergraduate examination structure. Adv Physiol Educ 2006;30:94-5.

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