INTRODUCTION

Nitric oxide (NO) represents one of the most versatile signaling molecules in biology, exerting crucial regulatory functions from the level of mitochondria and endothelium to complex neuronal networks. Since its discovery as the endothelium-derived relaxing factor, NO has evolved from a simple vasodilator to a central mediator integrating vascular, metabolic, and neural homeostasis. Its dual nature as both a cytoprotective and cytotoxic agent depending on concentration, localization, and source renders it an intriguing target across biomedical disciplines. The contributions gathered in this special issue of *Physiological Research* highlight the multifaceted role of nitric oxide in health and disease, spanning from basic molecular mechanisms to translational and clinical implications.

A review and experimental studies in this issue explore how NO interacts with other major biological systems and how these interactions shape cardiovascular, metabolic, and neural functions. Several articles address the intimate crosstalk between the nitric oxide pathway and the renin–angiotensin system (RAS), particularly under conditions of hypertension, diabetes, and viral infection. Paulis *et al*. [1] examined how combined pharmacological blockade of the RAS affects circulating and tissue levels of angiotensin peptides, revealing a complex redistribution between Ang II and the protective Ang (1–7) axis. Their results advocate for a balanced approach that maintains the endothelial-protective effects of the ACE2/Mas pathway, where NO serves as a downstream effector. In a related contribution, Pechanova and Paulis reviewed the involvement of NO in ACE2 biology and its implications for COVID-19 associated cardiovascular and neurodegenerative comorbidities [2]. By linking viral S-nitrosylation, endothelial dysfunction, and long-term cognitive consequences, their work underscores NO as a unifying factor in post-COVID vascular and neural pathology.

Other studies emphasize the importance of NO in metabolic and dietary interventions. Pechanova *et al.* [3] demonstrated that even short-term fructose exposure perturbs the NO/reactive oxygen species balance in hypertensive rats before overt hemodynamic changes occur, identifying the kidney as an early and sensitive target. Similarly, Saman *et al.* [4] investigated the interaction between NO and hydrogen sulfide signaling in obese diabetic rats treated with the sulfhydryl-containing ACE inhibitor zofenopril. Their findings indicate that restoration of both gaseous transmitter systems provides superior vascular protection, illustrating the therapeutic potential of dual NO/hydrogen sulfide modulation. Zemancikova *et al.* [5] added another dimension by showing that intermittent fasting induces long-lasting improvement in arterial reactivity mediated partly by perivascular adipose tissue and preserved NO-dependent relaxation even after return to ad libitum feeding. The role of metabolic disturbantion was also examined by Bozkurt *et al.* [6], who showed reduced NO production in the hearts and livers, and more pronounced vascular damage, in hyper-triglyceridemic rats compared with borderline hypertensive rats. Together, these studies highlight how dietary and metabolic factors alters cardiovascular function and how pharmacological agents converge on NO pathways to preserve vascular health and redox equilibrium.

The molecular interface between oxidative stress and inflammation is further explored by Cebova *et al*. [7], who demonstrated that blockade of high-mobility group box 1 after myocardial infarction restores endothelial NO synthase expression and activity, reduces pro-inflammatory cytokines, and enhances antioxidant defense. Similarly, Kluknavsky *et al*. [8] reported that acute stress and surgery downregulate nuclear factor erythroid 2-related factor 2 (NRF2) mRNA expression and disturb iron metabolism and oxidative balance in the liver of prehypertensive rats — processes closely intertwined with oxidative damage and inflammation. Taken together, these findings emphasize the pivotal role of redox-sensitive transcriptional networks in modulating NO bioavailability and vascular responses under stress, metabolic burden, or inflammation.

Beyond the cardiovascular domain, NO emerges as a crucial neuromodulator linking molecular mechanisms with cognition and emotion. In their philosophical–neuroscientific preface, Jagla and Pechanova [9] discuss NO as a biochemical substrate of experience, memory, learning, and attention, extending Locke's sensualistic concept into the realm of the biological foundations of the mind

and further to conditioned psychological and sociological activities related to perceived events. In a complementary experimental study, Vrankova *et al.* [10] demonstrate that post-weaning social isolation in rats reduces neuronal NO synthase activity, increases oxidative stress, and impairs behavior, supporting the hypothesis that NO deficiency contributes to stress-related cognitive and affective disturbances. These works underscoring NO essential role in transforming sensory input into memory and higher cognition.

The significance of NO in reproductive physiology is illustrated by Kuracinova *et al.* [11], who describe cyclic variations in endometrial NOS expression, linking NO to immune modulation, vascular remodeling, and implantation potential. Their observations suggest that physiological NO fluctuations may determine reproductive success, providing a framework for future therapeutic strategies in infertility. Finally, Gabor *et al.* [12] extend the relevance of nitric oxide and sensory modulation to neurorehabilitation, demonstrating that sensory-based postural training improves functional outcomes after stroke and highlighting the interplay between sensory input, motor control, and recovery.

Together, the studies presented in this special issue reveal nitric oxide as a molecular common denominator across organ systems and disciplines. From the modulation of vascular tone and metabolic adaptation to the encoding of memory and the orchestration of immune tolerance, NO exemplifies biological integration at its finest. The diversity of approaches, from molecular and cellular studies through integrative physiology to philosophical reflection, illustrates how NO research continues to transcend traditional boundaries between neuroscience, cardiovascular science, and behavioral medicine. This issue thus celebrates not only four decades of nitric oxide biology but also its continuing capacity to connect molecular mechanisms with the complexity of living systems.

This special issue of *Physiological Research* is dedicated to our colleague Fedor Jagla, MD, PhD on the occasion of his 80th birthday. His lifelong contribution to the study of higher brain functions, neurophysiology, and the philosophical dimensions of human cognition has inspired generations of physiologists and neuroscientists. As one of the pioneers of psychophysiological research in Slovakia, he has devoted his career to exploring how neural mechanisms underlie attention, perception, and imagination, while promoting an integrative understanding of the human mind and body. His leadership, intellectual curiosity, and humanistic perspective have profoundly shaped the scientific community and continue to influence new generations of researchers. His integrative view of the human mind as a bridge between biological processes and conscious experience beautifully mirrors the unifying essence of nitric oxide as a signaling molecule connecting the body and the mind.

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On behalf of the Special Issue editors

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