The 80th Birthday Anniversary of

Jozef Török

One of the outstanding scientists, Associate Professor of Physiology Jozef Török, MD, PhD, recently celebrated his 80th birthday. He was born on 25 March 1937 in Báb, Slovakia and completed the Medical Faculty of Comenius University in Bratislava, where he graduated with excellence in 1961. He started his scientific career at the “Institute of Experimental Medicine,” which was later renamed the Institute of Normal and Pathological Physiology Slovak Academy of Sciences (INPP SAS) and still exists today. He remained loyal to this institution during his entire scientific career.

At the beginning of the sixties when he began his professional work, cardiovascular research dominated problems related to the autoregulation of blood flow in different organs and its relation to an integrated organism. His thesis was devoted to hemodynamic problems of the canine small intestine and was titled “The effect of elevated venous pressure on hemodynamics of small intestine” which he defended in 1968. The study of the autoregulation of blood flow in skeletal muscle brought some new basal data regarding how the biomechanical parameters of blood flow affect the tone of vascular smooth muscle (Töröková et al. 1968). J. Török found that the contraction of resistant vessels in the small intestine was shown to be significantly greater in response to increased intravascular pressure if the elevation in blood pressure was induced from the venous portion (Török 1980, Török et al. 1984).

J. Török was greatly influenced by the international symposium “Circulation in Skeletal Muscle” that was organized by Olga Hudlická and Ján Gero in Smolenice in 1965, in which many prominent scientists from Europe and the USA also took part. Personal contact and friendship with scientists from foreign countries increased his interest in scientific work. Like all young investigators who are serious about building a career in research, he needed to gain experience working in an environment where the best intellects and equipment were present. Three years later, he again had the opportunity to meet some of these world leading physiologists in the USA. In 1968, J. Török left for the Department of Pharmacology at UCLA in Los Angeles, USA. He worked under the leadership of Prof. John A. Bevan, a distinguished personality and the scientist dealing with the function of the cardiovascular system and its vegetative nerve control. He was focused on the interaction between adrenergic nerves and vascular smooth muscles. He investigated the entry and movement of noradrenaline through the vessel wall and the early time course and distribution of both uptake processes (neuronal and extra-neuronal) of noradrenaline through the wall of the rabbit thoracic aorta using an original
isotopic frozen section technique (Bevan and Török 1970). He discovered that if both surfaces of the vessel were exposed to \(^3\)H-noradrenaline, tritium (\(^3\)H) accumulated at the adventitio-medial junction where sympathetic nerve terminals are mostly present. If only the intimal surface of the aorta was exposed, the \(^3\)H concentration was highest near the intima and in the center of the arterial wall. Tritium entering through the adventitia rapidly filled part of the extracellular space of the tunica and was collected in the junctional area (Török and Bevan 1971). These data made it possible to calculate the apparent diffusion coefficient for \(^3\)H-noradrenaline in the extracellular space of the media.

The scientific knowledge of J. Török increased during his long-term stay in the USA, and his international contacts and relationships could have become remarkable. During that time, he gained contacts and friendships with world-leading physiologists, such as J. A. Bevan, C. Su, O. A. Nedergaard, R. R. Sonnenschein, R. F. Furchgott, A. P. Somlyo, C. Hyman, and others. After returning to Slovakia, J. Török became one of the enthusiasts involved in the development of scientific life in Slovakia within the frames of the Slovak Academy of Sciences. He actively contributed to building and improving the physiological laboratories that were focused on research of the cardiovascular system. Within the framework of INPP SAS, he has become one of the leading personalities that determined the thematic orientation of the institute. J. Török introduced a new method for functional studies on the cardiovascular system that enabled the study of the activity of vascular smooth muscle on isolated preparations.

In 1972, J. Török became the Head of the Department of Cardiovascular Physiology and actively contributed to improving the working conditions and supply of research laboratories. Despite difficult traveling abroad, he made an effort to create international cooperations at least with the institutions in eastern European countries. In the eighties, the main research interest of J. Török was adrenergic control of the cardiovascular system and its modulation by vasoactive drugs. According to his findings, the neuroeffector junction between the adrenergic endings and the vascular smooth muscle cells represents a vital link in the generation of vasomotor responses, and it can be modulated by local physical, chemical and pharmacological events (Török 2006). He also studied the potentiating and inhibiting effects of various drugs on the adrenergic contraction of blood vessels. Serotonin, at the threshold concentration, amplified the contractile responses evoked by nerve stimulation and exogenous noradrenaline in the pulmonary and mesenteric arteries (Török 1999). Carbamate local anesthetics (pentacaine and heptacaine) inhibited neurogenic contractions and those elicited by exogenous noradrenaline and KCl. It is suggested that carbamate local anesthetics inhibit not only neuronal conductance but also Ca\(^{2+}\) entry into the vascular smooth muscle cells and the noradrenaline-induced release of intracellular Ca\(^{2+}\) (Török et al. 1986). These results conform with the hypothesis that the inhibition of vascular contraction is caused by the competitive antagonism between Ca\(^{2+}\) and aminoglycoside antibiotics (streptomycin, neomycin, and kanamycin) at the binding sites of excitable membranes (Török and Törökóvá 1986). Török (2006) summarized his own results using many other drugs and factors modulating the adrenergic contraction of smooth muscles in selected conduit arteries and veins, including adenine nucleotides and nucleosides, divalent cations (barium, strontium, magnesium, cadmium, manganese, nickel and zinc), hyperosmolarity, etc.

Participation of the vascular endothelium in the control of smooth muscle tone was studied more intensively in INPP SAS after 1985. J. Török, in a close cooperation with his coworkers (Vladimír Smieško, Anna Holécyová and others), investigated the reactivity of the rabbit abdominal aorta 4 days after endothelial removal (Török et al. 1985, Holécyová et al. 1985). The endothelium and its function in an organism has become the main research topic in this institute for more than 30 years. Professor R. F. Furchgott, a father of the “endothelium-derived relaxing factor,” personally visited the institute in 1991 and supported the effort of scientific workers for continuing this research. Later, J. Török evaluated the functional properties of endothelial cells in various animal vessels and during different conditions and diverse stages of ontogenic development. With his colleagues, he determined that whereas short-term cold storage at 4 °C caused no change, prolonged storage (two days and more) attenuated the endothelium-dependent vasorelaxation of the rat thoracic aorta in spite of the unaltered enzymatic process (Török et al. 1993). While the endothelial cells were very fragile and susceptible to cold treatment, cold storage by itself did not affect the production of nitric oxide (NO), one of the most important vasodilators (Kristek et al. 1993). Similarly to a longer cold exposure of isolated vascular preparations,
the exposure of rabbits to prolonged passive smoking also impaired the endothelium-dependent vasorelaxation of isolated arteries (Török et al. 2000). He also contributed to the elucidation of cardiovascular control during the ontogenesis. Together with Mária Gerová, he described the developmental dynamics of the endothelial and neurogenic control of conduit arteries in dogs. He discovered that in the perinatal period, the extent of endothelium-dependent relaxation and neurogenic constriction of the thoracic aorta displayed an opposite trend: acetylcholine-induced relaxation was already fully operative in fetuses and puppies, and its extent was declining toward adulthood, whereas the neurogenic constriction showed the highest values in adults (Török and Gerová 1996, Török and Gerová 1997). Knowledge of the appropriate receptors in the endothelium provides a suitable tool for studies on the specificity of mechanisms leading to NO production. These results indicated that the inactivation of one type of endothelial receptor did not interfere with the endothelial capability to produce and/or release NO by activation of other types of receptors and that the contemporary activation of different endothelial receptors could account for a reserve mechanism of NO-mediated relaxation (Kyselá and Török 1996, Kyselá and Török 2000).

In the next series of experiments, J. Török expanded his research area to different aspects of chronic NO-deficiency and an associated model of NO-deficient hypertension. He showed that a chronic inhibition of NO-synthase produced, aside from hypertension, an increased vascular responsiveness to α-adrenergic agonists in arteries that had low-pressure (pulmonary artery) and high-pressure (thoracic aorta) circulatory systems, suggesting that the restriction of NO rather than the difference in receptor sensitivity between both agents in normotensive conditions (Török 2000). Endothelial NO may also be involved in the regulation of neurogenic responses of blood vessels. Endothelial removal or inhibition of NO synthase by L-NAME enhanced the contractile responses of the rabbit carotid artery to an electrical field stimulation at normal conditions as well as at a reduced temperature (Kyselá and Török 1997).

NO-deficient hypertension can already be demonstrated in the early postnatal period. However, the endothelium-dependent relaxations of different conduit arteries (aorta, carotid and pulmonary arteries) were only slightly attenuated in newborn dogs and in rats that were chronically treated with an NO-synthase inhibitor, which probably reflects the preservation of high levels of NO-synthase activity in the arterial wall (Török and Gerová 1996, Gerová et al. 2002). In adult NO-deficient hypertensive rats, J. Török confirmed that the interruption of NO-synthase inhibition and a treatment with NO donors as well as with rilmenidine (an agonist of imidazoline receptors) revealed a beneficial and preventive effect on both blood pressure and functional changes of arteries (Török and Kristek 2002, Gerová et al. 2004). Additionally, NO-deficiency abolished the abnormalities observed during fructose administration in normal rats, suggesting that a functional NO system could be necessary for the manifestation of adverse effects of a high-fructose diet (Zemančíková and Török 2014, Zemančíková and Török 2015).

J. Török also reviewed the role of NO in other models of experimental hypertension (genetic and salt-dependent models) and contributed to the elucidation of NO-related mechanisms in different pathological stages (Török 2008). Hereditary hypertriglyceridemic (HTG) rats were developed as a genetic model of human metabolic syndrome with several metabolic abnormalities, such as hypertriglyceridemia, and with the elevation of blood pressure (Zicha et al. 2006). J. Török confirmed that HTG rats had impaired the endothelium-dependent vasorelaxation of different conduit arteries, which was accompanied by marked changes in the vascular architecture (Török et al. 2002, Török et al. 2007a, Šimko et al. 2005). The role of NO in spontaneously hypertensive rats (SHR), an animal model of human essential hypertension, is still a subject of debate. Nevertheless, J. Török and his colleague Frantisek Kristek confirmed that NO function remained unchanged in conduit arteries of SHR, indicating that NO production is probably a compensatory vasodilator system responding to hypertension (Török and Kristek 2001, Török et al. 2006). Preventive melatonin treatment of SHR in the early stage of its development resulted in a decreased increment of blood pressure and a slightly decreased neurogenic contraction but did not influence the acetylcholine-induced relaxation in the rat thoracic aorta. Nevertheless, the relaxation ability of the thoracic aorta of both non-treated and melatonin-treated rats was fully preserved, suggesting an intact NO signalization in
With his PhD student and subsequently his colleague Anna Zemančíková, J. Török was engaged in researching different areas of cardiovascular control in SHR. They have shown that during the rapid phase of pathological blood pressure increase in SHR, the chronic reduction of Ca\(^{2+}\) influx might eliminate the negative effect of enhanced sympathetic tone and lead to the reduction of increased neurogenic contractions (Zemančíková et al. 2008, Zemančíková and Török 2009). Increased sympathoadrenergic activity and enhanced Gi protein expression have been found in SHR, and Anna Zemančíková with J. Török and other co-authors showed that the inactivation of Gi proteins markedly diminished the effectiveness of adrenergic stimuli in the vasculature of SHR (Zemančíková et al. 2008). On the other hand, they indicated that hypertension may also lead to specific biomechanical alterations in diverse arterial types, which are reflected in different modifications of their contractile properties, including a compromised contractile function of elastic type arteries such as the thoracic aorta (Zemančíková and Török 2013). During the past few years, they focused on the investigation of the role of perivascular adipose tissue in the modulation of arterial contraction in normotensive and hypertensive individuals, which is a topic that appeared to gain an increasing attention from both experimental and clinical researchers. They confirmed that the impaired anti-contractile influence of perivascular adipose tissue in SHR might significantly contribute to the increased sensitivity of arteries to adrenergic stimuli (Török et al. 2016, Török and Zemančíková 2016).

In addition to his life-long position in the INPP SAS research institution, J. Török has been very active in teaching normal and pathological physiology courses at the Faculty of Natural Sciences of the Comenius University in Bratislava for more than 30 years. As a popular lecturer, he has positively influenced several generations of students. As an Associated Professor of Physiology, J. Török’s teaching involves lectures and courses for students as well as helping Master and PhD students with their theses (six students have completed their PhD degree under his personal supervision). He encouraged young students and scientists in their PhD studies to study new ideas and perspectives in physiological research and pathophysiological research. According to him, it is necessary to improve the cardiovascular program for students to reflect the many changes that have been obtained in scientific knowledge and to choose an effective way to better understanding of the physiology and pathophysiology of disease processes.

J. Török’s research interests focus on the regulation of vascular tone during normal and pathological conditions. His results were presented at various professional meetings and published in scientific journals, and they contributed significantly to a novel concept of cardiovascular regulation in health and disease. Dr. Török received several awards and medals, e.g. a silver plaquette of J. Jesenius, a memorable medal of J. E. Purkyňe, a gold medal from the Medical Faculty Comenius University, a gold medal from the Slovak Physiological Society, and a silver medal from the Faculty of Natural Sciences Comenius University of Bratislava. The extraordinary scientific skills, academic enthusiasm, and commitments and contributions of J. Török were also appreciated at the international symposium “Heart, Brain and Blood Vessels” that was held in April 4-5, 2017 in the Congress Centre of the Slovak Academy of Sciences in Smolenice. The appreciation for his contribution to the sciences and physiological society were also expressed by front leaders of the Czech and Slovak Physiological Societies, including Josef Zicha MD, DSc, Managing Editor of Physiological Research, Prof. Jaroslav Pokorný, MD, DSc, President of the Czech Physiological Society, Prof. Andrea Čalkovská, MD, DSc, President of the Czech Physiological Society, and many other excellent scientists from Slovak and Czech Republic who were present at the symposium.

Doc. MUDr. Jozef Török, CSc belongs to the group of great contributors to our knowledge on the physiology of neurogenic control in the vascular system. Throughout his long career dedicated to experimental research, J. Török made many highly innovative and valuable (thematic) contributions to normal and pathological physiology and pharmacology of the cardiovascular system. His working enthusiasm, creative ideas, unceasing activity and broad collaborations are inspiring for his pupils, collaborators and friends. As an experimentalist who made the majority of his investigations on experimental models, he always declares the necessity to study a living organism in its complexity (including cardiovascular regulations) as it undergoes profound changes in the course of its ontogenesis. He is a propagator of original scientific results obtained in the INPP SAS. J. Török is an extremely helpful man and belongs to a group of
friendly men who are always willing to do their best for others. He is still very active during his retirement and has accomplished remarkable results in many areas, and he enjoys his freedom to follow his own schedule with regard to scientific work and his own hobbies. All of us collaborators sincerely wish him all the best. May the angels watch over him and bring him strong health, successful work and pleasant adventures in both his professional life and private life.

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References


