

Zofia Zukowska

Bruce McEwen¹

The death of Zofia Zukowska, on April 15, 2012, represents the loss of a vibrant and energetic leader in the fields of stress physiology and neuropeptide Y (NPY) biology.



I first became aware of Zofia's innovative work on the function of neuropeptide Y (NPY) outside the brain through her ground-breaking *Nature Medicine* paper, in 2007, entitled "Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome" (Kuo et al., 2007). Prior to this, it was well known that NPY could inhibit excitation and seizure activity, and act as an anxiolytic agent in the brain (Heilig and Widerlöv, 1995; Bowers et al., 2012). Zofia's work helped to shed light on the negative aspects of NPY actions, which manifest especially when the system is dysregulated by stress. Indeed, her discovery that NPY is a growth factor that causes angiogenesis and adipogenesis, as well as contributes to atherosclerosis, represented a paradigm shift in the field, particularly with respect to understanding the mechanisms by which stress can lead to pathophysiology.

Zofia showed a remarkable ability to integrate various fields of knowledge. She initially studied cardiovascular medicine and obtained her PhD in Warsaw, Poland. She then pursued research on stress and the sympathetic nervous system in the United States, where she trained with influential scientists, including Irwin I. Kopin and Julius Axelrod of the National Institutes of Health. She joined as faculty at Georgetown University in 1985, later rising to Professor and Chair. In 2010, she moved to the University of Minnesota to become Professor in the Department of Integrative Biology and Physiology, and Director of a new and impressive Stress Physiology Center.

Zofia's diverse scientific background, as well as her ability to incorporate new concepts while still keeping the big picture in view, served her well as she explored new territory. Because of her curiosity and desire to integrate ideas, Zofia continued throughout her career to venture into different areas of science and to explore new methodologies. She had excellent judgment and a remarkable ability to identify collaborators with expertise in areas that were important and complementary to her own research. For example, the work in her landmark *Nature Medicine* paper was made possible through collaboration with Richard Kvetnansky from the Slovak Republic, an expert in sympathetic nervous system pharmacology and molecular biology, and Herbert Herzog from Australia, an expert in NPY genetics. Her collaborators from Georgetown University also included members of multiple departments.

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Zofia continued to study NPY until her untimely death earlier this year. She explored the role of NPY in the proliferation and differentiation of stem cells and intended to also investigate epigenetic and genetic factors that affect NPY expression, using transgenic mice and agents that alter histone acetylation and DNA methylation. She also translated findings in this area to study the association between obesity and post-traumatic stress disorder (PTSD). For example, Zofia co-authored a paper that examined the apparent increase in metabolic syndrome in people with PTSD; this relationship might be related to the altered sympathetic reactivity associated with that disorder and the altered stress sensitivity (Rasmusson et al., 2010). In that paper, the following hypothesis was advanced, which reflects, in part, Zofia's contribution to this collaborative study based on her highly developed knowledge of sympathetic nervous system function, and the sophistication of her thinking: "In general, then, NPY behaves like a high-pressure valve – inhibiting the release of [norepinephrine] during low sympathetic system activity and potentiating its impact during high activity. NPY thus conserves bioenergy for periods of high demand, at which point it helps to maintain organism function as energy and neurotransmitters are depleted [...] Lower NPY levels in persons

¹Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, The Rockefeller University, 1230 York Avenue, New York, NY 10065, USA
e-mail: mcewen@mail.rockefeller.edu

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with PTSD could, therefore, be expected to lower the stress threshold and increase the frequency of NPY release. A compelling hypothesis thus emerges. The frequency with which NPY and other stress reactants are released into the fat, as well as the amplitude of release may critically contribute to the risk for metabolic syndrome. This may help explain why PTSD severity influences the risk for metabolic syndrome [...] and why individuals without PTSD who carry neuroprotective gain-in-function NPY polymorphisms that increase the amplitude of NPY release [...] are also at risk. The risk for metabolic syndrome in the psychologically resilient would be expected to increase with exposure to repeated unconditioned stressors in objectively threatening environments, such as war zones. In PTSD, lower amplitude NPY stress responses may occur at high frequency in reaction to overgeneralized, conditioned threat cues in environments that are objectively safe, thus multiplying risk over time" (Rasmusson et al., 2010).

Some of her most recent investigations focused on the effects of maternal nutrition and stress on the metabolic health of offspring (Han et al., 2012), a topic that she intended to review in this special issue of

Disease Models & Mechanisms. Remarkably, she discovered sex differences in the effects of exposure to a low-protein diet during gestation; female offspring developed abdominal obesity whereas male offspring were unaffected. By contrast, cross fostering to mothers fed a normal diet caused the males to develop glucose intolerance and abdominal obesity, but did not affect female offspring. In that paper, Zofia and her co-authors also report that, in their pilot studies, "prenatal [low-protein diet] stress increased anxiety in male offspring, with lower NPY levels in the amygdala". This brings the story back to the anxiolytic and stress-reducing role of NPY in the brain, noted above, and the authors went on to write: "Thus, understanding the role of NPY mechanisms in brain areas related to anxiety will be an important direction of our future research" (Han et al., 2012). Hopefully, Zofia's colleagues will follow this exciting line of research in their future work, as the trade-offs of NPY action between reducing anxiety and promoting obesity are a fascinating biological issue that is relevant to modern society (Jackson et al., 2010).

It is clear from Zofia's career path that she adapted well to different cultures and languages and overcame many obstacles in

her research, and, I am sure, in many other aspects of her life. She was also dedicated to family and is survived by her husband, a daughter, a son, a stepdaughter and many friends. We salute her memory and shall miss her!

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