Obituary of Professor Kazuyoshi Tsutsui

Prof. Kazuyoshi Tsutsui passed away on September 16, 2021, aged 68 years. Kazuyoshi Tsutsui was born on September 30, 1952, in Hiroshima, Japan. Ever since his time in junior high school, he was greatly interested in biology, especially in the metabolic and endocrine systems. He entered the Department of Biology at Waseda University, Tokyo, Japan in 1972. He graduated from the University and entered its graduate school in 1976. He was awarded the degree of Doctor of Science as the representative of all PhD students from Waseda University in 1981. He mainly studied the effect of follicle-stimulating hormone and testosterone on the testis of Japanese quail during his graduate school years under the supervision of Prof. Susumu Ishii. He also studied and published the effects of sex steroids on the aggressive behavior of adult male quail, which is a work that is still frequently cited [1].

He was then employed by the Faculty of Science at Hiroshima University as a Research Associate under Prof. Seiichiro Kawashima in 1983. He was also a Postdoctoral Scholar of the Department of Neuroscience, University of Southern California, USA, from 1988 to 1989. Later, he was employed by Kobe University School of Medicine as an Assistant Professor in 1991. There, he developed his studies on gonadotropins in mammals, such as rats, mice, and hamsters [2, 3]. He was also interested in the seasonal regulation of the endocrine system and used songbirds as models [4, 5].

Prof. Tsutsui was employed by the Faculty of Integrated Arts and Sciences at Hiroshima University as an Associate Professor in 1993, and was promoted to Professor

in 1996. He was also the Director of the Center for Integrative Brain Sciences at Hiroshima University in 2000. It was during this time when he first discovered that neurons in the brain biosynthesize various neurosteroids *de novo* in birds and mammals [6–8]. He was also interested in the identification and functional analysis of various neuropeptides during this time [9–11].

He discovered gonadotropin-inhibitory hormone (GnIH) from the quail brain and demonstrated its inhibitory effect on gonadotropin release from the quail pituitary in 2000 [12]. The location of GnIH neurons and GnIH neuronal fiber distribution was studied in detail in the quail brain [13] and the GnIH receptor was also identified [14]. It was also shown that GnIH inhibits gonadal development and maintenance by inhibiting gonadotropin synthesis and release in the male quail [15]. It was further demonstrated that a pineal hormone melatonin induces the expression of GnIH in the quail brain [16].

Prof. Tsutsui also studied the physiological function of neurosteroids in the brain, such as the effects of progesterone and estrogen on the development of Purkinje neurons [17–19]. He further identified a novel neurosteroid, 7 α -hydroxypregnenolone, which acts as a neuronal activator of locomotion by means of the dopaminergic system in newts [20].

In 2006, Prof. Tsutsui returned to the Department of Biology, Waseda University, after Prof. Sakae Kikuyama's retirement. He continued studies on GnIH mainly through collaboration with not only Japanese but also foreign scientists. The inhibitory effect of GnIH on go-

gonadotropin release in mammals was first shown in hamsters by collaboration with scientists at the University of California at Berkeley [21]. GnIH was identified and their physiological functions were shown in hamsters [22], sheep [23], macaque monkeys [24], and humans [25]. It was also shown that GnIH has inhibitory effects on socio-sexual behavior in birds [26–28] and mammals [29, 30]. The molecular mechanism of the inhibitory effect of GnIH on gonadotropin gene expression was shown in immortalized gonadotrope cells [31].

It was suggested from morphological studies that GnIH regulates GnRH neurons by direct innervation and expression of the GnIH receptor on GnRH neurons in birds [32] and mammals [22]. The direct effect of GnIH on GnRH expression and release was clearly shown using immortalized GnRH cells [33]. It was also shown that melatonin not only stimulates GnIH expression but also its release in quail [34]. Interestingly, the expression of GnIH was stimulated by stress and corticosterone, suggesting that GnIH is involved in the inhibitory mechanism of stress in reproduction [35]. GnIH was also expressed in gonads and regulates sex steroids biosynthesis in birds [36] and mammals [37]. Prof. Tsutsui was also interested in the molecular evolution of GnIH [38–41].

He continued the studies of neurosteroids and found that 7 α -hydroxypregnenolone mediates melatonin action on diurnal locomotor rhythms [42]. It was shown that 7 α -hydroxypregnenolone might stimulate upstream migration by means of the dopaminergic system in salmon [43]. He studied the effect of pineal allopregnanolone on Purkinje cell survival [44] and brain development [45]. He was also interested in kisspeptin, a neuropeptide that stimulates GnRH neurons [46, 47]. Recent studies of GnIH by Prof. Tsutsui include the effect of norepinephrine and thyroid hormones on GnIH expression and release [48, 49].

Prof. Tsutsui became the Emeritus Professor of Hiroshima University in 2013 and returned to the Graduate School of Integrated Sciences for Life at Hiroshima University as a Specially Appointed Professor in 2020. He received numerous honors during his career, including the Zoological Society Prize from the Zoological Society of Japan in 2001, Yoshimura Prize from the Japan Society for Pituitary Research in 2008, Farner Medal from the International Society for Avian Endocrinology in 2008, Masao Ito Best Presentation Award from the Society for Research on the Cerebellum in 2011, Bargmann-Scharrer Award from the International Federation of Comparative Endocrinological Societies (IFCES) in 2013, Okuma Prize for Science and Technology from Waseda University in

2015, Prize for Science and Technology, The Commendation for Science and Technology from the Minister of Education, Culture, Sports, Science, and Technology, Japan in 2015, and Kobayashi Award from the Japan Society for Comparative Endocrinology in 2016.

Prof. Tsutsui was very committed to various Japanese and international scientific organizations. He was President of the Japan Society for Pituitary Research in 2005, Vice-President of the Zoological Society of Japan from 2016 to 2018, President of the Japan Society for Avian Endocrinology from 2006, President of the Japan Society for Comparative Endocrinology from 2006 to 2010, President of the Asia and Oceania Society for Comparative Endocrinology from 2009 to 2018, President of the International Society for Avian Endocrinology from 2013 to 2016, Vice-President of the International Federation of Comparative Endocrinological Societies from 2013 to 2016, and President of the International Federation of Comparative Endocrinological Societies from 2017.

He was also a member of the editorial board of various scientific journals, such as *Neuroendocrinology Letters*, *Zoological Science*, *Japanese Journal of Reproductive Endocrinology*, *Animal Cells and Systems*, *Journal of Experimental Neuroscience*, *Open Journal of Neuroscience*, *Clinical Immunology*, *Endocrine and Metabolic Drugs*, *Hormonal Studies*, *BioMed Research International*, *Physiology Journal*, *PeerJ*, *Journal of Neuroendocrinology*, *Endocrinology*, *General and Comparative Endocrinology*, *Frontiers in Integrative Pharmacology*, *Frontiers in Neuroendocrine Science*, *Frontiers in Experimental Endocrinology*, *Brain, Behavior and Immunity*, *Scientific Reports*, *The European Journal of Zoology*, and *Current Neurobiology*. He was the Editor-in-Chief of *Comparative Endocrinology* from 2000 to 2005, Editor-in-Chief of the *Japanese Journal of Reproductive Endocrinology* from 2008 to 2019, and Editor-in-Chief of *Neuroendocrinology* from 2020.

He supervised seven PhD students, Kazuyoshi Ukena, Dan Li, Hirotaka Sakamoto, Takayoshi Ubuka, Masahiro Matsunaga, Tomohiro Osugi, and Shogo Haraguchi, as their main theses advisor. The names of his recent collaborators are H. Vaudry, J.C. Wingfield, G.E. Bentley, L.J. Kriegsfeld, P.J. Sharp, I.J. Clarke, R.P. Millar, S.A. Sower, Y. Muneoka, V.S. Chowdhury, J.F. Cockrem, E. Saigoh, Y.L. Son, Y. Tobar, H. Yin, K. Inoue, H. Teranishi, Y. Fukuda, T. Mizuno, M. Narihiro, K. Ishikawa, S. Ishii, O. Koizumi, M. Ueno, H. Minakata, H. Satake, E. Iwakoshi, D. Dauks, K. Gazda, T. Kosugi, G. Bedecarrats, M. Hisada, T. Kawada, N.L. McGuire, R. Calisi, N. Perfito, S. O'Brien, I.T. Moore, J.P. Jensen, G.J. Kaur, D.W. Wacker, N.A. Ciccone, I.C. Dunn, T. Boswell, S. Kim,

Y.C. Huang, J. Reid, J. Jiang, P. Deviche, T.W. Small, M.A. Ottinger, T. Tachibana, M. Furuse, M.A. Cline, D.F. Mei, A. Mason, E.M. Gibson, S.A. Humber, S. Jain, W.P. Williams III, S. Zhao, I.P. Sari, Y. Qi, J.T. Smith, H.C. Parkinson, J. Iqbal, Q. Li, A. Tilbrook, K. Morgan, A.J. Pawson, M. Murakami, T. Matsuzaki, T. Iwasa, T. Yasui, M. Irahara, M.A. Johnson, G.S. Fraley, H. Oishi, C. Klausen, C.B. Gilks, T. Yano, P.C.K. Leung, M. Binns, P.A. Cadi-gan, H. Lai, M. Kitani, A. Suzuuchi, V. Pham, S. Ki-kuyama, K. Yamamoto, A. Koda, I. Hasumuma, F. Toyoda, K. Sawada, K. Tsunekawa, P. Singh, S. Anjum, A. Krishna, R. Sridaran, S. Sethi, C.M. Chaturvedi, M.R. Ja-farzadeh Shirazi, M.J. Zamiri, A. Tamadon, M. Amano, S. Moriyama, M. Iigo, K. Uchida, M. Nozaki, H. Kawauchi, M. Shahjahan, T. Ikegami, H. Okamura, H. Doi, A. Hat-tori, H. Ando, Y. Honda, Y. Inai, K. Inoue, H. Miyabara, T. Koyama, Y. Ogura, S. Suzuki, S. Hara, M. Kusaka, Y. Suzuki, M. Mita, K. Sasahara, H. Shikimi, S. Honda, N. Harada, M. Hatori, M. Takase, T. Hirota, M. Iitsuka, N.

Kurabayashi, K. Kokame, R. Sato, A. Nakai, T. Miyata, Y. Fukada, Y. Yamamoto, J.H. Chang, M. Sato, H. Ueda, K. Tashiro, T. Tokita, J.Y. Seong, J.L. Do Rego, J. Leprince, G. Pelletier, E.E. Baulieu, and others.

Prof. Tsutsui had not been feeling well since April 2021 and had been undergoing treatment for esophageal cancer at Hiroshima University Hospital since May 14 this year. His funeral was held in Hatsukaichi City, Hiroshima on September 18. His family received numerous condo-lence letters not only from Japan but also from the USA, the UK, Europe, India, Malaysia, and other countries and regions. He was an excellent mentor, colleague, and friend to many of us. We admire his scientific achievements and are sincerely grateful for his leadership in science. We be-lieve he is now peacefully resting in heaven with his be-loved wife Rieko, who passed away 8 years ago.

September 2021

Takayoshi Ubuka, Gan Medical Service Co. Ltd
Kazuyoshi Ukena, Hiroshima University

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