LEGENDS IN UROLOGY

Toichi Takenaka, D.V.M. & PhD
Chairman of the Board
Astellas Pharma Inc.
Tokyo, Japan

It was a great honor when The Canadian Journal of Urology invited me to contribute a paper to Legends in Urology. I was hesitant at first, because I am not an urologist, but a pharmacologist. However, I was encouraged to write about my discovery of tamsulosin (Flomax®, Harnal®, Omnic®), because it changed the treatment of benign prostatic hyperplasia (BPH). This is the story of bench to bedside research, and I decided to write this paper to encourage future generations of scientists to pursue their instincts and dreams.

In the early 1960s when I was still a veterinary student at Gifu University, I was very impressed by a lecture on adrenoceptors (AR). In 1948, Ahlquist hypothesized that there were two adrenoceptors; α- and β-ARs.[1] His hypothesis was later verified by the discovery of α-AR and β-AR antagonists. These two antagonists were developed as effective medications for the treatment of hypertension. I became increasingly interested in pharmacology because I believed it could validate biological response mechanisms using chemical compounds, and that these compounds could then serve as treatments to alleviate suffering from disease.

After graduation in 1964, I joined Yamanouchi Pharmaceutical Co., Ltd. I was assigned to the drug discovery research team for cardiovascular treatment. In the 1970s, β-AR antagonists were promoted as breakthrough therapy for hypertension. They had some limitations, because they had a slow onset of action and a low response rate. These were due to the fact that β-AR antagonists do not lower peripheral vascular resistance. α-AR antagonists, on the other hand, do lower peripheral vascular resistance. This led to the idea that a compound blocking both α-and β-ARs could serve as the more effective antihypertensive treatment. Our team embarked on designing such a drug. In 1958, dichloroisoproterenol (DCI), the first β-AR antagonist, was synthesized by chemically modifying the β-AR agonist, isoproterenol. To obtain a new combined α- and β-AR antagonist, we used a similar approach in drug design by synthesizing and screening many derivatives of noradrenaline, an α- and β-AR agonist. In 1976, we discovered amosulalol, which blocks both α1-AR and β-AR receptors. Since this drug was later launched under trade name Lowgan™ to treat hypertension, I decided to expand my research to other areas. However, since my scientific interest remained with ARs, I continued to search for new applications.

As I was searching the literature, I came across interesting papers by Caine and his colleagues. In around 1975, they described the distribution of α-ARs in the smooth muscles of the prostate and reported that phenoxybenzamine (POB), a nonselective α-AR antagonist, was effective in treating symptomatic BPH.[2,3] At that time, α-ARs were pharmacologically classified into two subtypes, α1 and α2. In collaboration with Dr. Kawabe, in the Department of Urology, The University of Tokyo, we demonstrated that the α-AR which controls the contraction of human prostatic smooth muscles was the α1-subtype, and not the α2-subtype.[4] Acting on this finding, we began to search for a new type of selective α1-AR antagonists as a therapeutic agent for the voiding dysfunction associated with BPH. This was my motivation to pursue uro-pharmacology and neuro-urology.

Chemical studies with the enantiomers of amosulalol led to the design of a new type of α1-AR antagonist. R(-)-isomer of amosulalol showed β-AR blockade, whereas the S(+)-isomer showed selective α1-AR blockade. We then synthesized and screened many derivatives of S(+)-amosulalol and discovered tamsulosin in 1980.[5] Tamsulosin is a new chemical class of potent and selective α1-AR antagonist with a structure different from that of POB, prazosin and terazosin. We investigated tamsulosin to discern the mechanism of its therapeutic action. An anesthetized-dog model showed that the α1-AR antagonism of tamsulosin was more pronounced in the urethra

than in blood vessels. Again, *in vitro* receptor binding assays using membrane preparation of human tissues revealed that tamsulosin has a 10 times higher affinity for prostate tissue than for blood vessel tissue. In contrast, prazosin showed no selectivity between these tissue types. In this way, tamsulosin was found to have different pharmacological characteristics from existing α1-AR antagonists. In other words, it had prostate tissue selectivity, and therefore we proceeded into clinical trials.

In an initial randomized, double-blind, placebo-controlled study of Japanese patients with BPH, conducted by Kawabe et al, tamsulosin was found to be extremely effective for treating symptomatic BPH without affecting blood pressure and causing orthostatic hypotension.[6] Successive clinical studies conducted in Europe and the U.S. also produced results identical to Kawabe's study in terms of efficacy and safety.

Pharmacological and clinical studies conducted between 1975 and 1993, determined that tamsulosin has functional selectivity for the prostate. It was still not clear, however, why tamsulosin was so tissue-specific. In the 1990s, receptor research began to be conducted at the gene level; and it became possible to clone receptor-subtype genes. At least three subtypes of α1-ARs have been identified: α1A, α1B and α1D. α1A-ARs are predominant and responsible for contraction in the human prostate, whereas α1B-ARs are responsible for vasoconstriction. The expression of α1A-AR messenger in human prostatic tissue with BPH was also significantly higher than that in non-BPH tissue. These studies on receptor-subtype genes suggest that increased expression of the α1A subtype may be primarily responsible for the prostatic contraction in BPH patients. The affinity of various α1-AR antagonists in cloned α1-AR subtypes was evaluated by Michel.[7] Tamsulosin showed an affinity for α1A-ARs that was 30 times higher than that for α1B-ARs. Meanwhile, conventional α1-AR antagonists, prazosin and terazosin, showed no difference in affinity for the two α1-AR subtypes. Thus, about 10 years after the discovery of the compound, we determined that the molecular mechanism of tamsulosin's prostate selectivity was derived from its high affinity for α1A-ARs.

The evolution of medical treatments has made remarkable strides thanks to advances in the technology used in drug discovery. In the 1960s, advances in pharmacology led to a clearer understanding of the function of ARs. This breakthrough paved the way to the discovery of tamsulosin.

In the 1990s, the advent of molecular cloning techniques enabled many receptor molecules to be classified. This finding helped clarify tamsulosin's molecular mechanism of action. I am truly grateful for opportunity to continue my research on ARs, in which I took an interest during my student days 50 years ago, and to have been involved in the discovery of the urological drug, tamsulosin and the cardiovascular drug, amosulalol. I am also deeply grateful to Dr. Kazuki Kawabe, emeritus professor of the Department of Urology, The University of Tokyo, for instructing me in urological treatment when I only knew about AR pharmacology.

Finally, I would like to mention that tamsulosin's U.S. patent ends this year. My research on uro-pharmacology and neuro-urology also seems to be reaching its final days. It is time to welcome a new generation or researchers who will carry on the mission of drug discovery, translational research in urology and medicine, for the betterment of the patient.

Toichi Takenaka, D.V.M. & PhD
Astellas Pharma Inc.
Nihonbashi-Honcho, Chuo-ku, Tokyo, Japan

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