DISCOVERY OF RAMELTEON AS A NOVEL MELATONIN RECEPTOR AGONIST, THAT INDUCES NATURAL SLEEP

Shigenori OHKAWA
Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited

Good quality sleep is an essential requirement for leading an active and fulfilling life. However in today's society where lifestyles have become more complex and varied, many people tend to understate its importance and sacrifice sleep in favor of efficiency or profit. As a result, many people in industrialized countries suffer from sleeping disorders, which are now becoming a major social issue. Considerable research has been conducted on the physiological implications of sleep, which cover a broad range of functions in addition to rest for the brain and the body, such as memory retention, maintaining immune system function, providing energy for thinking and day time activity. Taking this into account, what does a drug for sleeping disorders require?

Over the last hundred years various pharmaceutical products have been developed to successfully treat a number of medical needs. This is especially true in the field of lifestyle-related diseases, where it is now possible to reduce blood pressure, blood-sugar level and cholesterol level to normal by using antihypertensive drugs such as angiotensin-receptor antagonists (ARB), hypoglycemic drugs such as PPARγ agonists and cholesterol-reducing drugs such as statins. However the true endpoint of those drugs is not to reduce these indices, but to reduce the risks of severe cardiovascular diseases like cerebral infarction and myocardial infarction and to improve mortality and quality of life by preventing sight loss and nervous disorders, which occur as complications in lifestyle-related diseases.

Taking this point of view, the endpoint of the ideal sleeping disorder drug should be to induce natural sleep and also to maintain at their normal level the many functions that are supported by sleep. However, although $GABA_A$ agonists, such as the representative drug benzothiazepine are now commonly used, they have not reached the level to fully satisfy the market. Sleep induced by a $GABA_A$ agonist is not natural sleep and also leads to various adverse effects such as impairment of memory and motor functions. Because of this situation, a programme was started to discover a new class of drug for sleeping disorders based on the concept of "induction of natural sleep", which after 12 years of research and development resulted in the launch of a melatonin receptor agonist (trade name Rozerem) as the world' first nonscheduled drug.

I think that a clear concept, that is supported by correctly recognized pathological condition and treatment paradigm, and a commitment to research are important to discover good drugs. I would like to introduce how I got the idea for the sleeping disorder drug Ramelteon and its research, development and approval.