Adenosine Transporters in Cardiovascular System

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After graduating in Pharmacy at the Chinese University of Hong Kong in 1997, George Leung worked as an intern for one year in hospitals and got the qualification of a registered pharmacist. Then he pursued his PhD at the Department of Physiology, The Chinese University of Hong Kong, followed by two years' post-doctoral training at the Department of Medicine, The Johns Hopkins University. He joined the Department of Pharmacology, The University of Hong Kong as Research Assistant Professor in 2003.

His main research area is in the understanding of nucleoside transporters. His group is one of the first to clone and study equilibrative nucleoside transporter (ENT)-3 and concentrative nucleoside transporter (CNT)-3. He also studies the regulation of nucleoside transporters in physiological and pathological states. Besides, he is attempting to discover novel inhibitors for nucleoside transport. These studies will likely add new knowledge on the development of cardiovascular protective agents.

He was the recipient of the Young Physiologist Scheme of the Physiological Society of UK in 1999. He is currently the treasurer of the Asian Society for Vascular Biology. He is also the members of various societies such as the American Physiological Society, Society for the Study of Reproduction and Hong Kong Pharmacology Society.

Adenosine is an endogenous purine nucleoside and modulates a variety of physiological functions by interacting with cell surface adenosine receptors. Under adverse conditions such as ischemia, hypoxia, stress and inflammation, extracellular levels of adenosine are increased. The increased extracellular adenosine protects tissues from excessive damage. It has been demonstrated that adenosine attentuates the ischemic heart injury, reduces inflammation and is vasodilatory. However, the therapeutic application of adenosine is limited because extracellular adenosine usually disappears quickly due to its rapid uptake into adjacent cells and subsequent metabolism.

Adenosine is taken up from the extracellular space into adjacent cells through the nucleoside transporters on plasma membrane. Two major classes of nucleoside transporters in mammalian cells have been characterized by Na^+-dependence. The equilibrative nucleoside transporters (ENTs) are facilitated-diffusion systems and are Na^+-independent. They are subdivided into two types. ENT1 is potently inhibited by a nanomolar concentration of nitrobenzylmercaptopurine riboside (NBMPR) but ENT2 is resistant to NBMPR up to 1 μM. Both ENT1 and ENT2 are broadly-selective, accepting both purine and pyrimidine nucleosides. In contrast, the concentrative nucleoside transporters (CNTs) are Na^+-dependent. They are subdivided into three types based on the substrate selectivity. CNT1 is pyrimidine nucleoside-selective; CNT2 is purine nucleoside-selective while CNT3 is broadly-selective.

ENT1 and ENT2 are the major nucleoside transporters found in heart and vascular smooth muscle cells. Interestingly, those transporters can be up-regulated by glucose, possibly via mitogen-activating protein kinase (MAPK)-dependent pathways. It may affect the availability of adenosine in the vicinity of adenosine receptors and thus, alter cardiovascular functions in diabetes. Pharmacologically, in addition to NBMPR and dipyridamole which are known nucleoside transport inhibitors, glitazones used in diabetes and many classical calcium channel antagonists are also able to inhibit adenosine transport. Nucleoside transport inhibitors can retard the disappearance of extracellular adenosine, elevate extracellular concentrations of adenosine, and enhance the protective effects of endogenous adenosine in tissues. As a result, nucleoside transport inhibitors are expected to exhibit ameliorating effects in various cardiovascular diseases.