PI: GPH LEUNG (PHARMACOLOGY)
Research theme: vascular biology

Description of research programme:

Physiology and pharmacology of nucleoside transporters

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 attenuates 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. Different types of nucleoside transporters in mammalian cells have been characterized. Equilibrative nucleoside transporter (ENT)-1 and ENT-2 are the major nucleoside transporters in heart and vascular smooth muscle. One of my research focuses is on the physiological and pathological regulations of ENT. We have found that ENT-1 transporters in vascular smooth muscle cells can be up-regulated by glucose, possibly via the 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. Another research focus is on the pharmacology of nucleoside transporters. We search for novel ENT inhibitors. In addition to nitrobenzylmercaptopurine riboside (NBMPR) and dipyridamole which are known ENT inhibitors, other compounds such as calcium channel antagonists (dihydropyridine type), glitazones and isoflavonoids are also able to inhibit ENT. We study the structure-activity relationship of those compounds. We modify their chemical structures in attempt to increase their specificity and potency on ENT. ENT 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, ENT inhibitors are expected to exhibit ameliorating effects in various cardiovascular diseases.

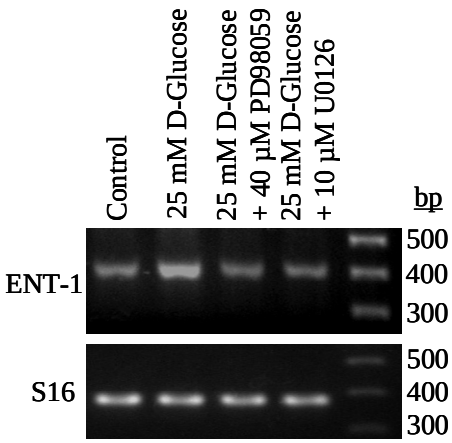

Fig. 1. Up-regulation of ENT-1 in vascular smooth muscle cells is inhibited by U0126, an MAPK inhibitor.

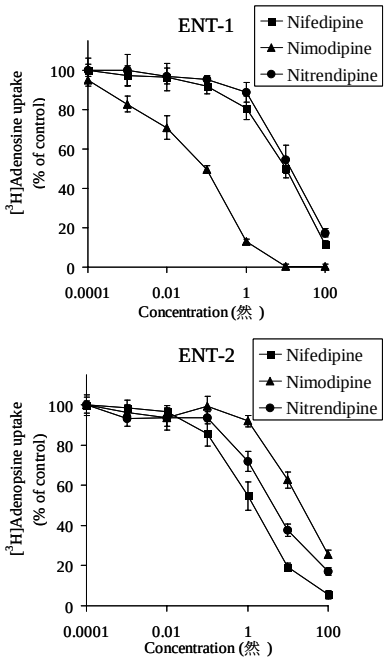

Fig. 2. ENT-1 and ENT-2 activities are inhibited by dihydropyridine type of calcium channel antagonists.

3 recent publications:

1. **Leung G.P.H.**, Tse, C.M. & Man R.Y.K. (2006) Characterization of adenosine transport in H9c2 cardiomyoblasts. *International Journal of Cardiology*, in press.
2. **Leung G.P.H.,** Man R.Y.K. & Tse, C.M. (2005). Effect of Thiazolidinediones on Equilibrative Nucleoside Transporter-1 in Human Aortic Smooth Muscle Cells. *Biochemical Pharmacology* 70: 355-362.
3. **Leung G.P.H.**, Man R.Y.K. & Tse, C.M. (2005). D-Glucose up-regulates adenosine transport in cultured human aortic smooth muscle cells. *American Journal of Physiology Heart Circulation Physiology*, 288, H2756-2762.