

Development of Anti-Ischemic Agents

Sung-Eun Yoo*, Kyu Yang Yi, Sunkyung Lee, Nak Jeong Kim, Jee Hee Suh,
Hwa Sup Shin, Byung Ho Lee, Sun Ok Kim

*Korea Research Institute of Chemical Technology, Taejon
DongBu-Hannong chemical, Co., Taejon, Korea*

It has been well known that ATP-sensitive potassium channel (KATP) openers have protective properties on the ischemia-reperfusion injury independent of their vasorelaxant effects. The vasodilating properties may mask the protective effects due to underperfusion of the tissue already at risk. Since the discovery of BMS-180448 as a cardioselective KATP channel opener, many efforts have been made to find more tissue selective KCOs (potassium channel openers) as well as to elucidate the structure activity relationships for the vasorelaxant and cardioprotective potencies, which are distinct.

In previous work, we discovered SK 450, a KCO with a potent vasodilating activity. Now, we turned our attention to explore the compounds with anti-ischemic properties. To this end, we have synthesized several classes of compounds; benzopyranyl guanidine derivatives, benzopyran derivatives substituted with secondary amines including heterocycles, benzopyranyl heterocycle derivatives, benzopyranyl phenylglycine derivatives, etc. Most compounds prepared, exhibited very weak or almost no vasorelaxation activity. There were compounds showing potent cardioprotective or neuroprotective effects from ischemia-reperfusion and hypoxic damages. In addition, some compounds showed protective activity against ischemic retina and impaired nociceptive responses in diabetic rats. Besides KATP channel opening properties, many compounds exhibited anti-oxidant properties such as suppression of lipid peroxydation, ROS formation, and NO generation, which may be beneficial for the treatment of ischemia-related diseases. Since cellular changes caused by ischemia are unlikely to have a single, discrete pathway, development of drugs acting on more than one target site may be beneficial.

In this talk, we will discuss about KR-31378 which shows potent cardioprotective and neuroprotective activities against ischemic-reperfusion and hypoxic damage or oxidative stress without vasorelaxation activity. This new chemical substance may be pharmacologically useful for the prevention and treatment of ischemic heart diseases, brain injury, and neurodegenerative disease, etc.