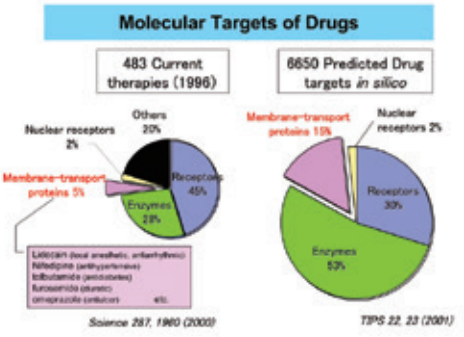
Department of Molecular Pharmacology

Professor: Shuji Kaneko, Associate Professor: Hisashi Shirakawa,
Assistant Professor: Kazuki Nagayasu

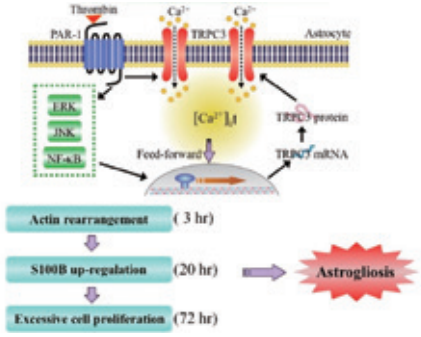
Research Projects:

A comprehensive analysis of molecular targets of drug therapy revealed that the largest subgroup is cell membrane receptors (45%), and the next is enzymes (28%), while membrane-transport proteins account for only 5% of all current drug targets; however, the drugs targeting membrane-transport proteins are strong, effective and frequently used in the therapeutic treatment. On the other hand, 6650 predicted proteins of potential drug targets are composed of 30% cell membrane receptors, 53% enzymes, and 15% membrane-transport proteins (see left panel). Consequently, it is considered that membrane-transport proteins will be the promising molecular targets of drug development. In our Department of Molecular Pharmacology, membrane-transport proteins, especially ion channels and transporters in the central nervous system, are focused on, and a variety of studies are in progress as follows:



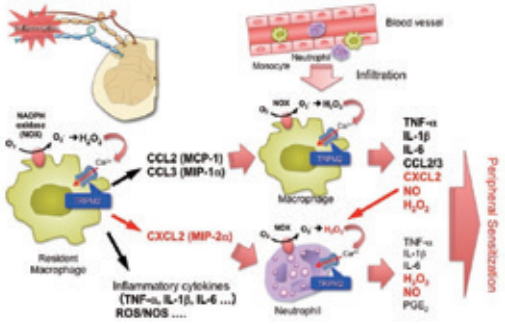
1) Study on the role of TRP channels involved in the pathophysiology of cerebrovascular diseases

Cerebrovascular diseases including cerebral infarction and intracerebral hemorrhage are severe neurological deficits in which generation of reactive radical moieties and inflammatory responses cause neuronal death and abnormal activation of glial cells after excessive overflow of neurotransmitters. On the other hand, TRP (transient receptor potential) channel is a family of nonselective cation channels, which may have important roles in nonexcitable cells, such as glial cells and immune cells. Therefore we focused on the mechanisms of abnormal glial activation that are involved in the chronic pathogenesis of cerebral stroke. So far, we have identified the pivotal role of TRPC3 in the thrombin-induced activation of astrocytes (see right panel). We now address the physiological and pathophysiological roles of other TRP channels in glial cells including astrocytes, microglia and oligodendrocyte precursor cells using genetically modified animals.



2) Study on the roles of TRP channels and transporters involved in the chronic pain

Injury of sensory neurons and surrounding inflammatory lesions cause chronic pain that is not always responsive to conventional analgesics. Since the mechanism underlying chronic pain is now well understood, we focused on the roles of glial cells and immune cells in the interaction with sensory neurons that aggravate pain sensation. We have clarified the role of astroglial glutamate transporter GLT-1 in the generation of neuropathic pain, and are investigating the algesic roles of TRPM2 expressed in monocytes/macrophages and microglia (see right panel). In addition, we are analyzing the involvement of TRP channels in the grave peripheral neuropathy induced by several kinds of antineoplastic agents such as oxaliplatin.



3) Study on the action mechanisms of antidepressants and addictive drugs

We have established an in-vitro chronic experimental system in which midbrain and limbic slices are cocultured for the study of addictive mechanisms of psychostimulants, narcotic analgesics, other addictive drugs such as MDMA on dopaminergic neuronal networks. We also developed an in-vitro raphe slice culture for the study of chronic effects of antidepressants such as SSRI, SNRI and tricyclic antidepressants on serotonergic neuronal networks.

Recent publications

- Munakata et al., Transient receptor potential canonical 3 inhibitor Pyr3 improves outcomes and attenuates astrogliosis after intracerebral hemorrhage in mice. **Stroke** 44, 1981-1987 (2013)
- Nagayasu et al., Chronic effects of antidepressants on serotonin release in rat raphe slice cultures: high potency of milnacipran in the augmentation of serotonin release. **Int J Neuropsychopharmacol**. 16, 2295-306 (2013)
- Zhao et al., Acute cold hypersensitivity characteristically induced by oxaliplatin is caused by the enhanced responsiveness of TRPA1 in mice. **Mol Pain**. 8, 55 (2012)
- Haraguchi et al., TRPM2 contributes to inflammatory and neuropathic pain through the aggravation of pronociceptive inflammatory responses in mice. **J Neurosci**. 32, 3931-3941 (2012)