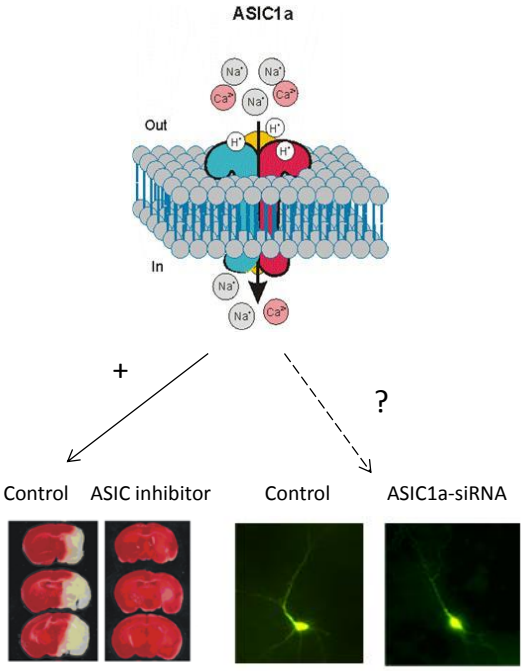
ASIC1a-activated Signaling Pathways in Neurons

Project director: Zhigang Xiong, M.D., Ph.D.

The acid-sensing ion channels (ASICs) are a family of proton-gated cation channels expressed throughout the nervous system [1]. They act as sensors of tissue pH. Although the exact physiological functions are yet to be determined, recent studies have demonstrated important roles for these channels in neurological disorders [2,3]. In particular, the involvement of ASIC1a channels in glutamate-independent neuronal injury associated with brain ischemia [2] has disclosed a novel therapeutic target for stroke [4,5]. Despite the major progress in identifying the pathological functions of ASIC1a channels, their physiological functions in the central nervous system (CNS) remain poorly defined. The present studies, using powerful proteomic analysis to rapidly and systematically identify the signaling pathways induced by ASIC1a protein expression and channel activation, followed by physiological characterization, will dramatically advance our understanding of the functions as well as regulations of these channels. Identifying ASIC1a-mediated signaling pathways specifically in pathological conditions will provide important information for the design of novel therapeutic interventions against neurological diseases without interfering with the physiological functions of these channels. Given the limitations of currently available inhibitors for this channel [6], defining the pathways specific to ASIC1a activation in pathological conditions may lead to alternative neuroprotective strategies.



Innovation: (1).The present studies, for the first time, will systematically define the signaling pathways induced by ASIC1a channels followed by studying the physiological functions of these channels. (2) The studies will utilize a combination of proteomics, molecular biology, pharmacology, neurophysiology, in vitro neuronal cell culture and in vivo animal models. (3). Using a combination of protein pull down assay and proteomic analysis, proteins that directly interact with or are tightly associated with ASIC1a proteins and thus may be involved in surface trafficking of the receptors will also be identified. (4) Defining signaling pathways specific to ASIC1a activation in pathological conditions is a novel approach to gain critical information for designing novel therapeutic strategies with minimal side effects.

1. Waldmann, R., Champigny, G., Bassilana, F., Heurteaux, C., and Lazdunski, M. (1997). A proton-gated cation channel involved in acid-sensing. *Nature.* **386**, 173-177.

2. Xiong, Z. G., Zhu, X. M., Chu, X. P., Minami, M., Hey, J., Wei, W. L., MacDonald, J. F., Wemmie, J. A., Price, M. P., Welsh, M. J., and Simon, R. P. (2004). Neuroprotection in ischemia: blocking calcium-permeable Acid-sensing ion channels. *Cell* **118**, 687-698.

3. Friese, M. A., Craner, M. J., Etzensperger, R., Vergo, S., Wemmie, J. A., Welsh, M. J., Vincent, A., and Fugger, L. (2007). Acid-sensing ion channel-1 contributes to axonal degeneration in autoimmune inflammation of the central nervous system. *Nat.Med.* **13**, 1483-1489.

4. Huang, Y. and McNamara, J. O. (2004). Ischemic stroke: "acidotoxicity" is a perpetrator. *Cell* **118**, 665-666.

5. Benveniste, M. and Dingledine, R. (2005). Limiting stroke-induced damage by targeting an acid channel. *N.Engl.J.Med.* **352**, 85-86.

6. Xiong, Z. G., Pignataro, G., Li, M., Chang, S. Y., and Simon, R. P. (2008). Acid-sensing ion channels (ASICs) as pharmacological targets for neurodegenerative diseases. *Curr.Opin.Pharmacol.* **8**, 25-32.