Joe McKenna, Membrane Biophysics, Fall 2014

Annotated Bibliography: Second-Messenger Gated Ion Channels

References

[1] FM Ashcroft and FM Gribble. ATP-sensitive K^+ channels and insulin secretion: their role in health and disease. *Diabetologia*, 42(8):903–919, 1999.

> This review summarizes the role of K_{ATP} channels in insulin secretion, namely their closure which initiates an electrical burst and Ca influx necessary for secretion. The article presents the structure of the ion channel, and focuses on the mechanism by which channel blockers such as sulphonylureas act to promote insulin secretion.

[2] Daniel L Cook and Nicholas Hales. Intracellular ATP directly blocks K^+ channels in pancreatic β-cells. 1984.

> This article is included in the references for historical perspective. It is a short letter to *Nature* describing the accidental discovery of K_{ATP} channels in pancreatic β-cells. The authors give the first physiological characterization of K_{ATP} channels with IV-curves and an ATP dose-response curve. They also propose what is now the widely accepted role of the channel in pancreatic β-cells, to couple the metabolic and electrical activity of the cell.

[3] Anna L Gloyn, Ewan R Pearson, Jennifer F Antcliff, Peter Proks, G Jan Bruining, Annabelle S Slingerland, Neville Howard, Shubha Srinivasan, José MCL Silva, Janne Molnes, et al. Activating mutations in the gene encoding the ATP-sensitive K^+-channel subunit Kir6.2 and permanent neonatal diabetes. *New England Journal of Medicine*, 350(18):1838–1849, 2004.

> This article uses a variety of techniques including genetic sequencing, targeted mutation, electrophysiology, and clinical observation to identify gene mutations that impair K_{ATP} channel function and cause neonatal diabetes. After identifying patients with neonatal diabetes and excluding those with genetic defects already known to correlate with the disease, the patients are examined and their genes which encode the Kir6.2 subunit of K_{ATP} channel protein are sequenced. Gene mutations and protein residue mutation positions are identified to inform models of K_{ATP} channel function that propose sites of ligand binding. Mutated channel proteins are reconstituted in oocytes and characterized by an altered dose-response to ATP.

[4] Michael V Mikhailov, Jeff D Campbell, Heidi de Wet, Kenju Shimomura, Brittany Zadek, Richard F Collins, Mark SP Sansom, Robert C Ford, and Frances M Ashcroft.

3-D structural and functional characterization of the purified K_{ATP} channel complex Kir6.2–SUR1. *The EMBO journal*, 24(23):4166–4175, 2005.

This article is a tour de force of structural biology of membrane proteins. Electron microscopy is used to elucidate the structure of K_{ATP} channels and overlay the imaged structure with current models. The authors observe a tightly packed configuration of four Kir and SUR subunits. They speculate the position of ATP binding at the interface of subunits and propose a conformation that conceals sequences allowing co-trafficking of Kir and SUR subunits to the membrane. They also offer the first structural insight into the Kir transmembrane domain 0 (TMD0) and first measurements of ATPase activity of the channel.

[5] T Miki, K Nagashima, and S Seino. The structure and function of the ATP-sensitive K^+ channel in insulin-secreting pancreatic β-cells. *Journal of molecular endocrinology*, 22(2):113–123, 1999.

This article focuses on the structure and function of K_{ATP} channels in pancreatic β-cells but also mentions the expression levels of subunit proteins in other cell types. The authors describe the molecular identity and structure of K_{ATP} channels and their role in transducing a stimulatory glucose signal to an insulin release signal. They also describe loss- and gain-of-function mutations in channel protein subunits that contribute to either hypo- or hyperglycaemia in mice.

[6] Takashi Miki, Kazuaki Nagashima, Fumi Tashiro, Kazumi Kotake, Hideyuki Yoshitomi, Atsuko Tamamoto, Tohru Gonoi, Toshihiko Iwanaga, Jun-ichi Miyazaki, and Susumu Seino. Defective insulin secretion and enhanced insulin action in K_{ATP} channel-deficient mice. *Proceedings of the National Academy of Sciences*, 95(18):10402–10406, 1998.

The authors assess the role of K_{ATP} channels in insulin release by measuring glucose-induced insulin release and insulin-regulated glucose uptake in mice genetically altered with loss-of-function mutations in the Kir6 subunits that form the pore of K_{ATP} channels in pancreatic β-cells. They notice, in the knockout mice, insufficient insulin release in response to glucose challenge and enhanced glucose uptake in insulin-dependent tissue. They propose a primary role for K_{ATP} channels in insulin release and a compensatory role of glucose uptake for the purpose of maintaining normoglycaemia in knockout mice.

[7] Colin G Nichols. K_{ATP} channels as molecular sensors of cellular metabolism. *Nature*, 440(7083):470–476, 2006.

This review article is the perfect entry point into the study of K_{ATP} channels since it provides an account of their structure and function in general terms. The author provides a contemporary model of the channel while highlighting

the major contributions and challenges that have been encountered up to the present. The relevance of the article is further realized in the conclusion when the author implicates channel malfunction in patients with diabetes and proposes future directions for the study of K_{ATP} channels.

[8] Patrik Rorsman, Lena Eliasson, Takahiro Kanno, Quan Zhang, and Sven Gopel. Electrophysiology of pancreatic β-cells in intact mouse islets of langerhans. *Progress in biophysics and molecular biology*, 107(2):224–235, 2011.

This review of electrophysiology of mouse pancreatic β-cells describes the ion channel activity that accompanies glucose-stimulated insulin secretion. In additon to K_{ATP} channels, voltage-gated K, Ca, and Na channels and Ca-activated K channels are described. The authors propose that K_{ATP} channels have multiple roles in regulating the electrical activity of pancreatic β-cells including stabilizing the membrane during silent phase, transiently depolarizing the membrane to elicit bursting during the active phase, and late reactivating during the active phase to contribute to bursting.

[9] Rona Sadja, Noga Alagem, and Eitan Reuveny. Gating of GIRK channels: details of an intricate, membrane-delimited signaling complex. *Neuron*, 39(1):9–12, 2003.

This is a short review of a particular type of second-messenger gated ion channel, namely G-protein coupled inward rectifier K channels. The article gives a description of their physiologicial role and outlines the progress that has been made at determining the structure of the channel protein and the site of second-messenger activation.

[10] Colin W Taylor, Stephen C Tovey, Ana M Rossi, Sanjurjo CI Lopez, David L Prole, and Taufiq Rahman. Structural organization of signalling to and from IP_3 receptors. *Biochemical Society transactions*, 42(1):63–70, 2014.

This article is a review of IP_3-regulated ion channels, second-messenger gated ion channels whose second messenger is the diffusible messenger IP_3. IP_3-regulated ion channels are primarily responsible for intracellular Ca motility and ulitmately shape Ca transients in cells with Ca channels. IP_3-gated channels are positioned to allow targeted delivery of Ca to organelles or the cell membrane. The article focuses on known substructures of the channel and the proposed mechanism of activation by IP_3.

Websites

1. http://www.youtube.com/watch?v=xF1rxn7yrPw - A lecture by a researcher from the Royal Society on her work with K_{ATP} channels and neonatal diabetes.

2. http://www2.montana.edu/cftr/ionchannelprimers/beginners4.htm - A rather long list of "Types of Ion Channels Known" from University of Montana with details on types of second-messenger gated ion channels.

3. http://www.ifc.unam.mx/Brain/secmen.htm - A primer on second-messenger gated ion channels in the brain.

4. http://www.cellsignallingbiology.org/csb/003/csb003.pdf - A freely available chapter published by the Journal of Biochemistry-sponsored organization Cell Signaling Biology on ion channels.

5. https://www.coursera.org/course/bioelectricity - A coursera course led by a emeritus professor at Duke covering the basics of bioelectricity and loosely based on his own text.

6. http://itb.biologie.hu-berlin.de/~stemmler/s4node4.html - An illustration and description of a second-messenger cascade.

7. http://courses.washington.edu/conj/gprotein/secondMess.htm - A page summarizing second messenger gated channels from a membrane biophysics course at University of Washington.

8. http://classes.biology.ucsd.edu/bimm118.WI12/PPT%20Lecture%20Notes/Lecture%204.pdf - Notes from a lecture at UCSD on second messenger gated ion channels.

9. http://www.ifc.unam.mx/Brain/secmen.htm - A site from a Spanish insitute focusing on second messenger-gated ion channels.

10. http://clinicaltrials.gov/show/NCT01934816 - An NIH site for recruiting clinical trial participants in a study aimed at better understanding K_{ATP} channels.