

Aug 31, 2003

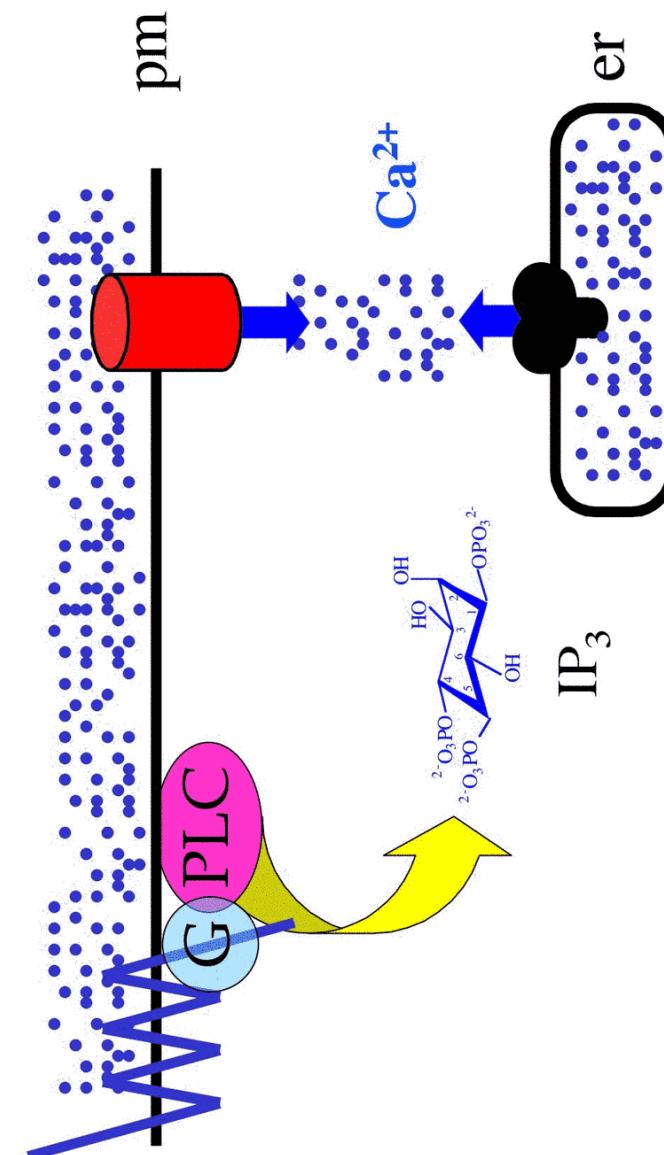
Regulation of IP₃ Receptors and Ca²⁺Entry Pathways

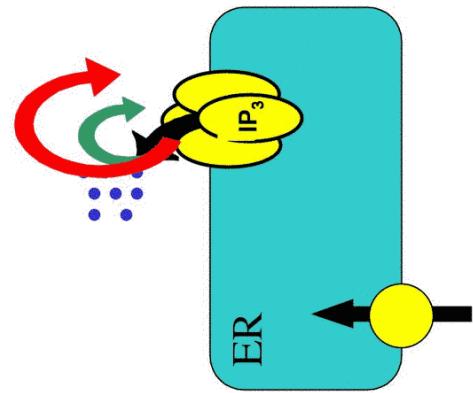
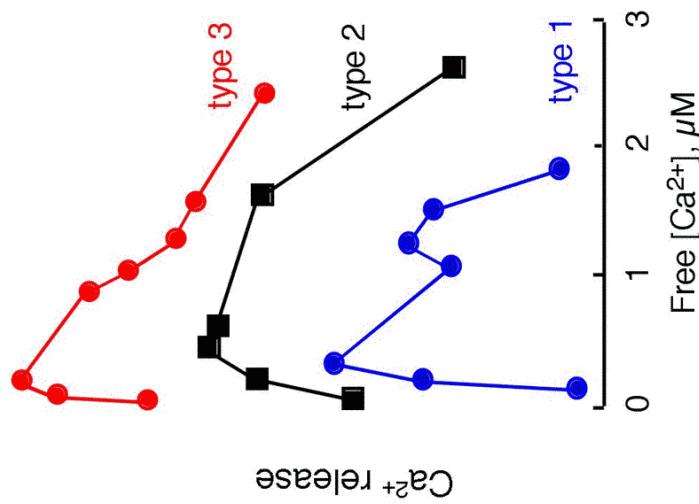
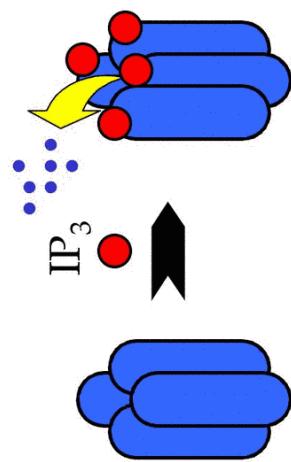
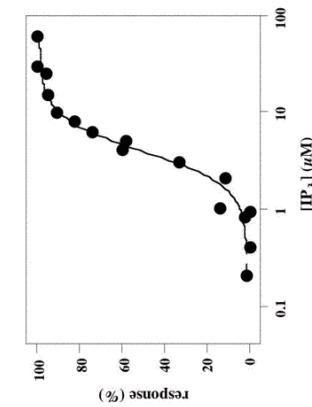
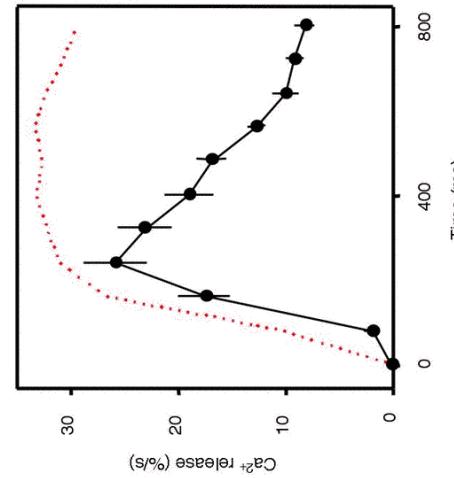
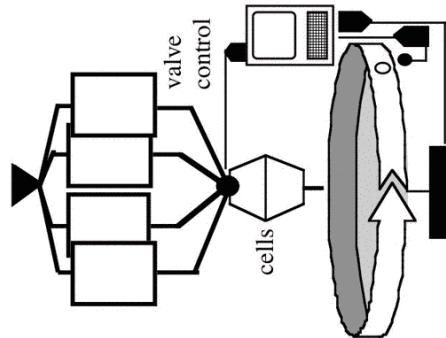
DR. COLIN W. TAYLOR

Department of Pharmacology
University of Cambridge

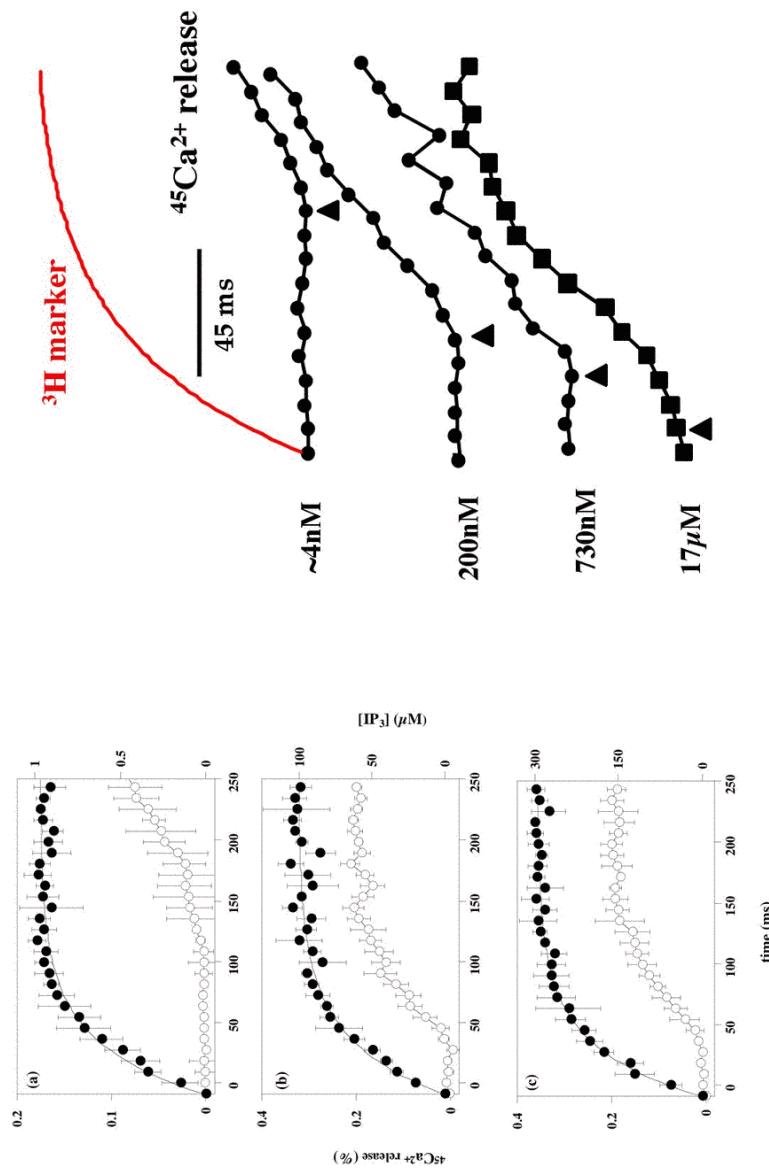
Biphasic effects of Ca²⁺ on IP₃ receptor function are common and widely supposed to contribute to the complex Ca²⁺ signals recorded from intact cells. I will present evidence from both functional and structural analyses of IP₃ receptors suggesting that IP₃ controls the opening of the channel by regulating Ca²⁺ binding to stimulatory and inhibitory Ca²⁺-binding sites. Ca²⁺ entry across the plasma membrane also contributes to the Ca²⁺ signals evoked by physiological stimuli. I will discuss recent results from A7r5 vascular smooth muscle cells showing that vasopressin reciprocally regulates Ca²⁺ entry through capacitative and non-capacitative Ca²⁺ entry channels via a signalling cascade that involves arachidonic acid, nitric oxide and cGMP.

Kavli Institute for Theoretical Physics
Symposium on Calcium Dynamics

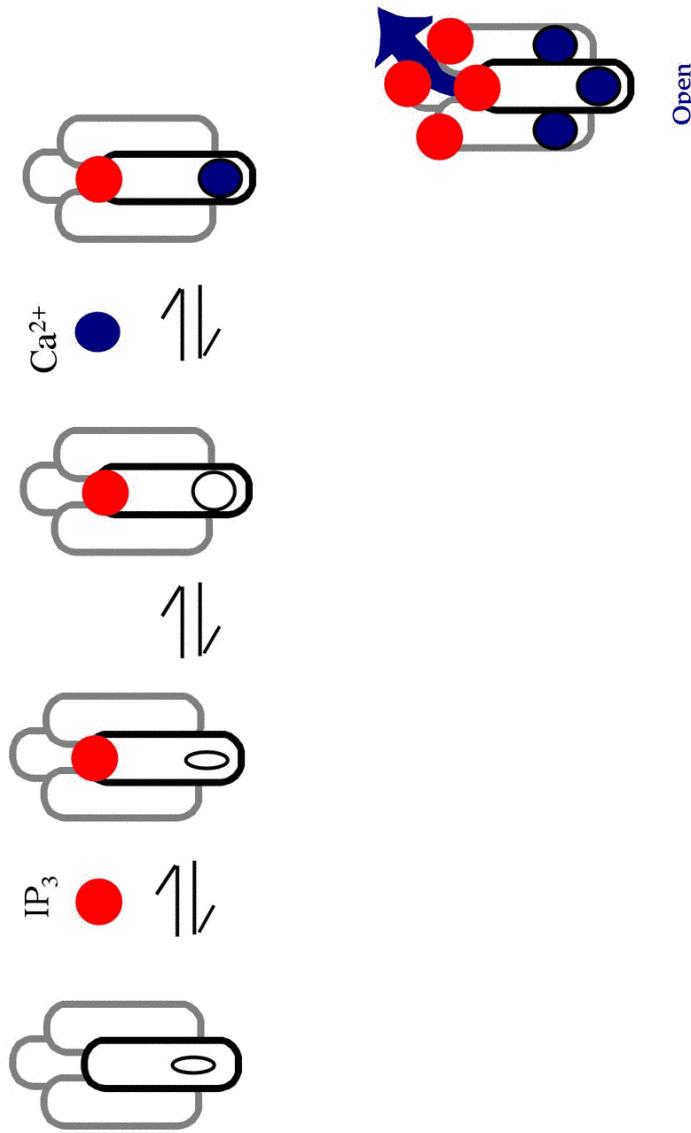


Biphasic regulation of IP₃ receptors by Ca²⁺**Rapid kinetics of IP₃-evoked Ca²⁺ release**

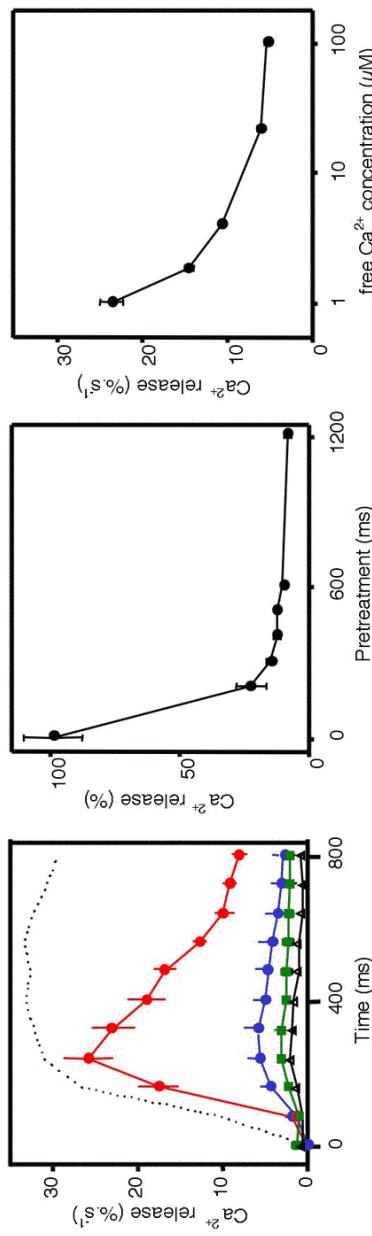
Delayed opening of IP₃ receptors



Sequential binding of IP₃ and then Ca²⁺

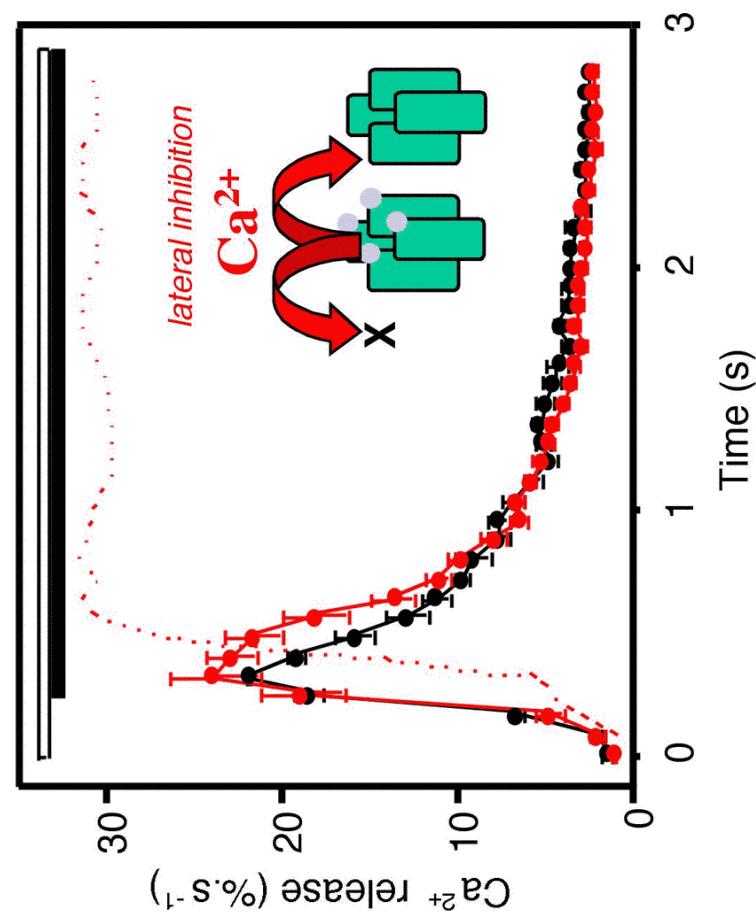


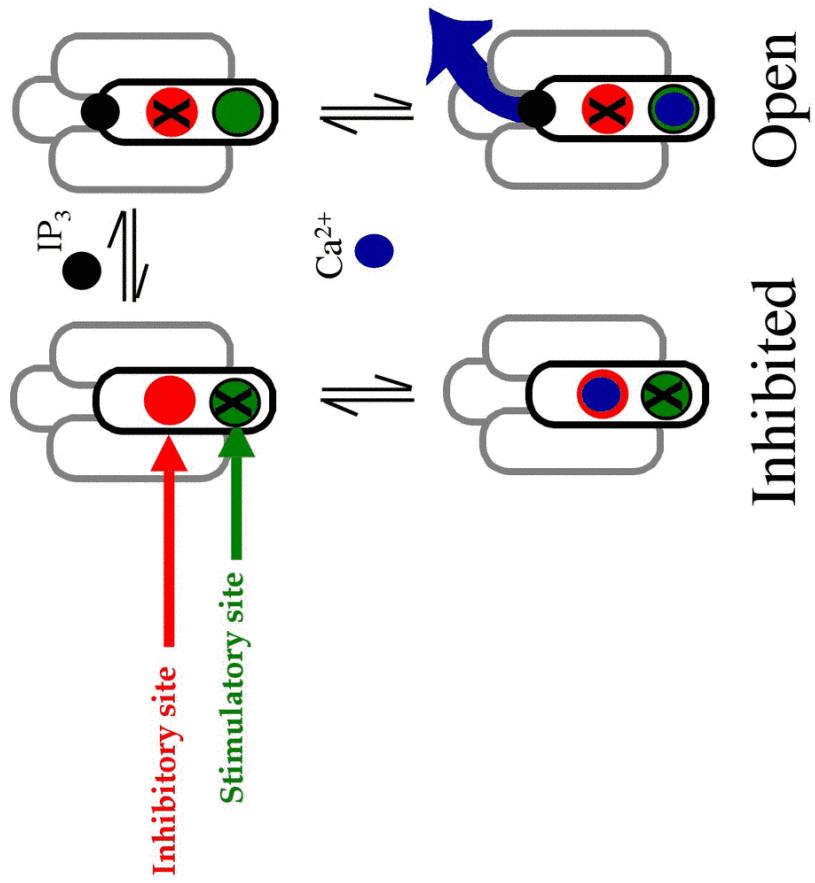
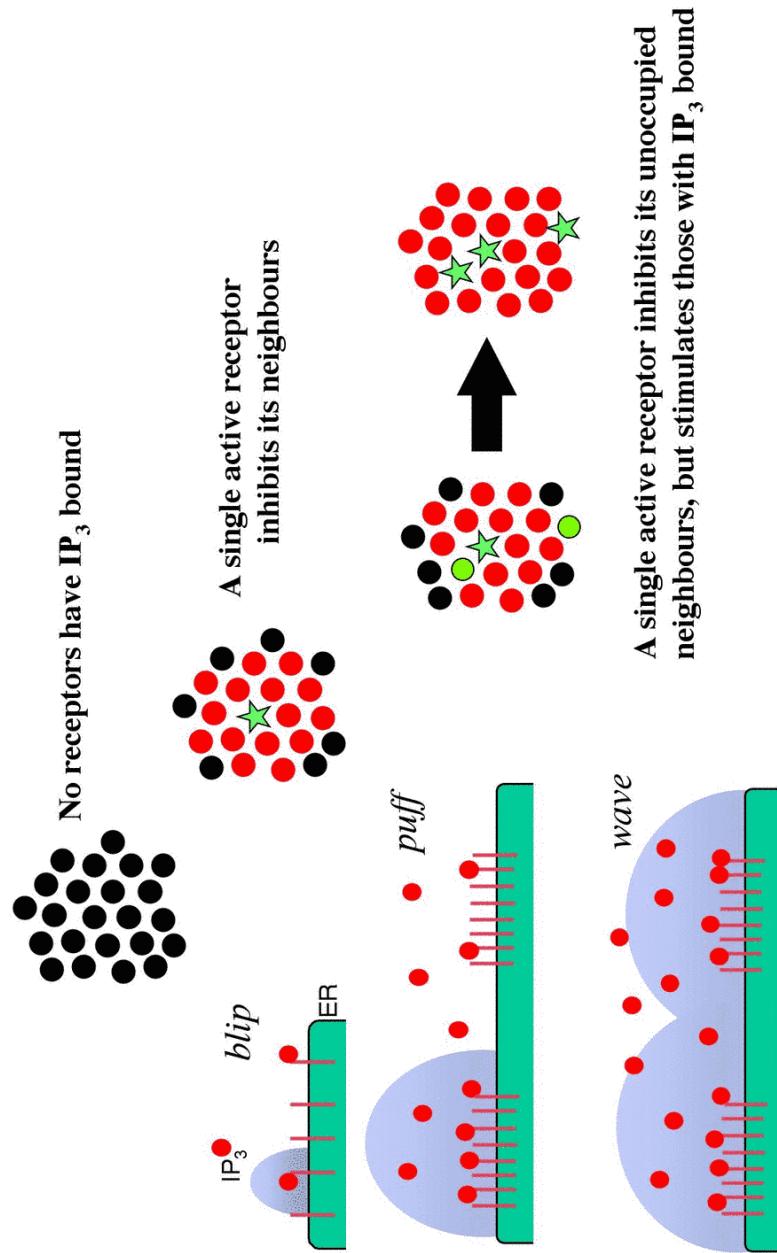
Rapid inhibition of IP₃ receptors by pre-treatment with high Ca²⁺

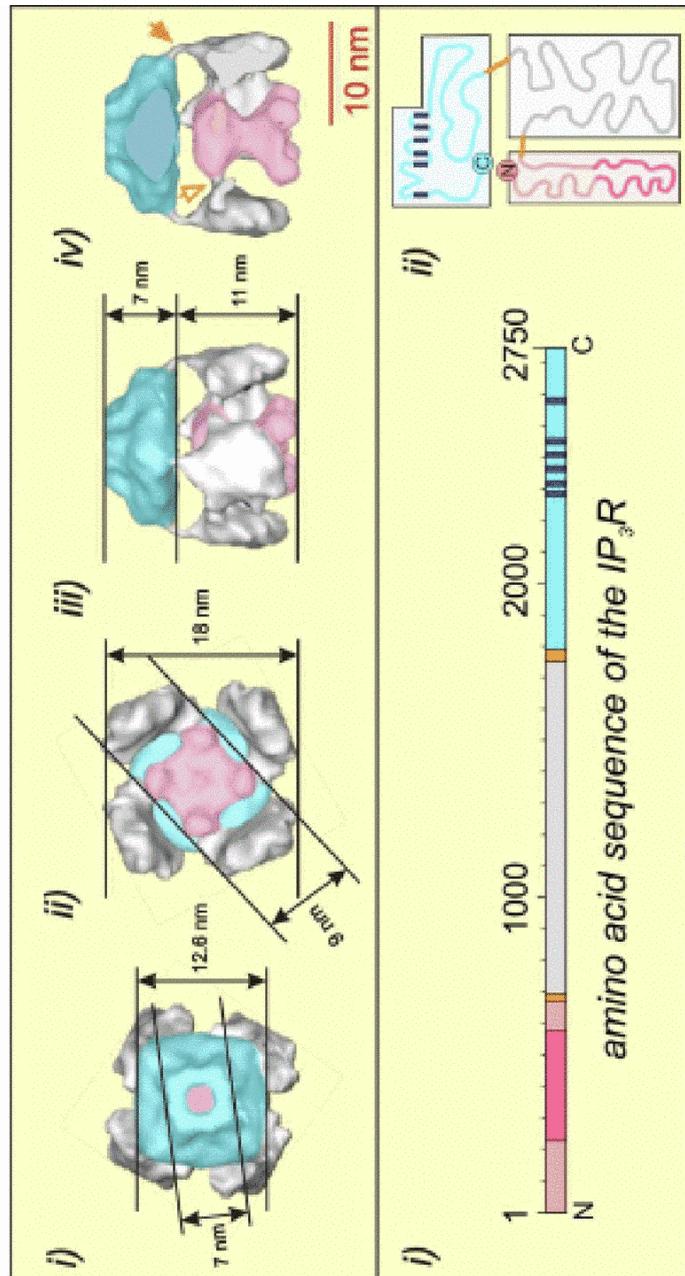
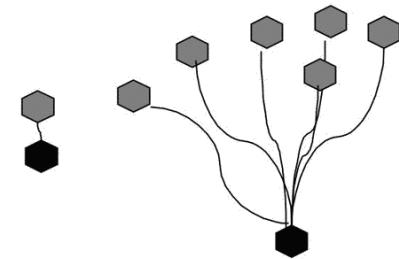
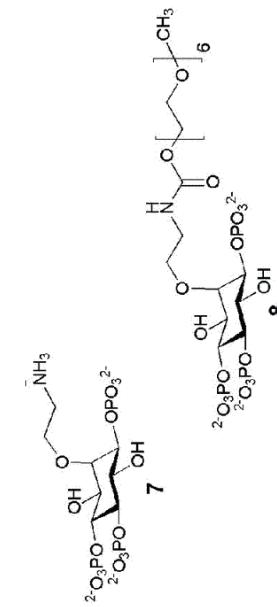
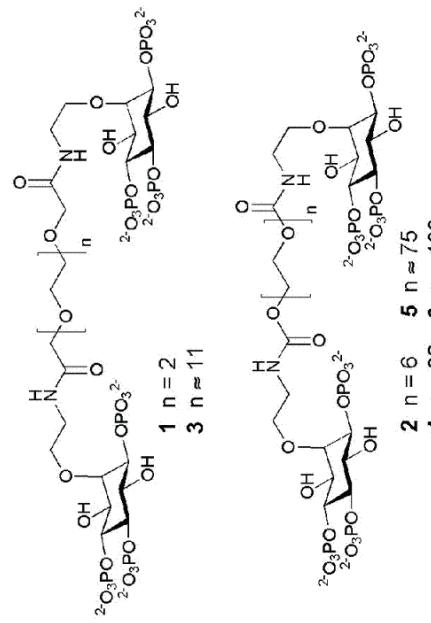
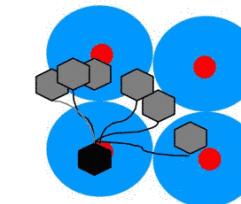


.....but slow recovery.....

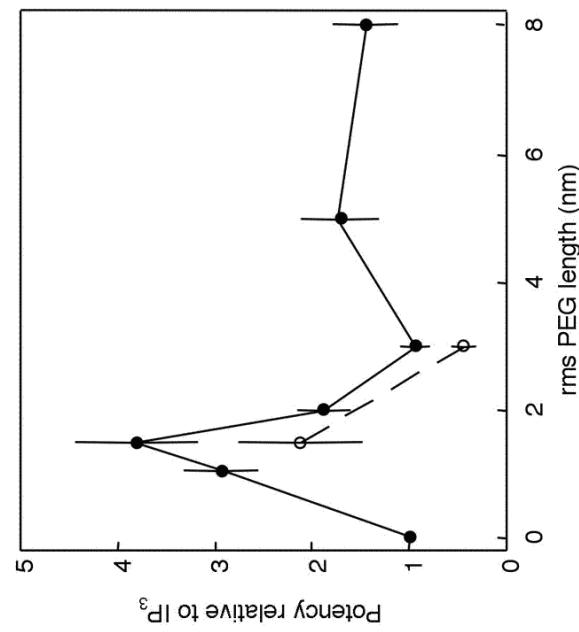
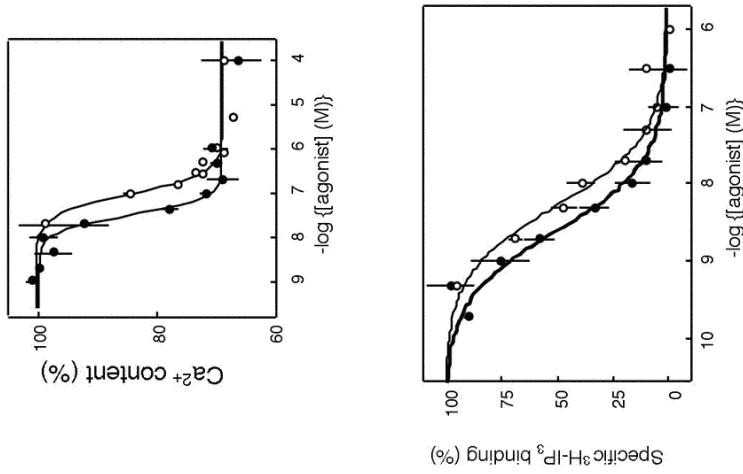
High Ca²⁺ does not inhibit receptors with IP₃ bound



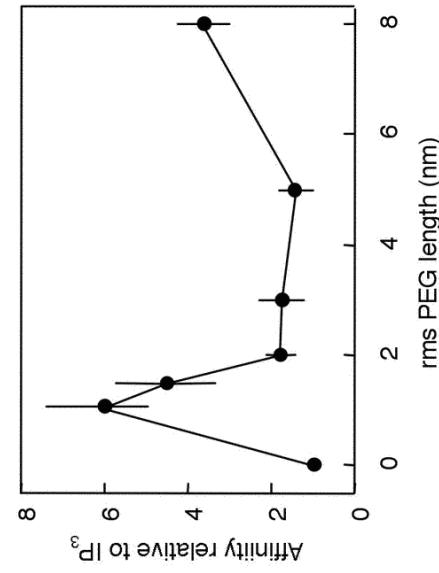
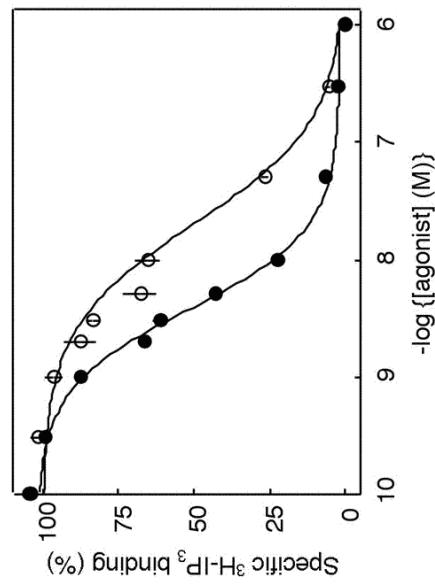
IP₃ controls what Ca²⁺ does to IP₃ receptorsLateral inhibition of IP₃ receptors by cytosolic Ca²⁺

Structure of type 1 IP₃ receptor at 30 Å resolution from EM-image analysisDimers of IP₃: molecular rulers

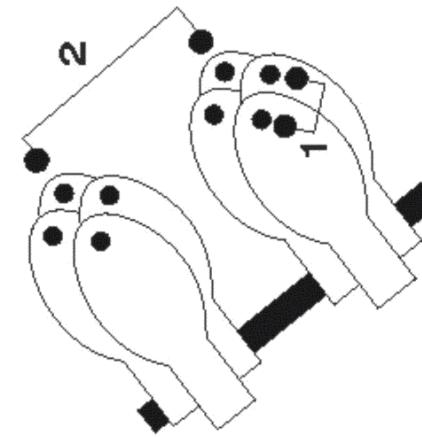
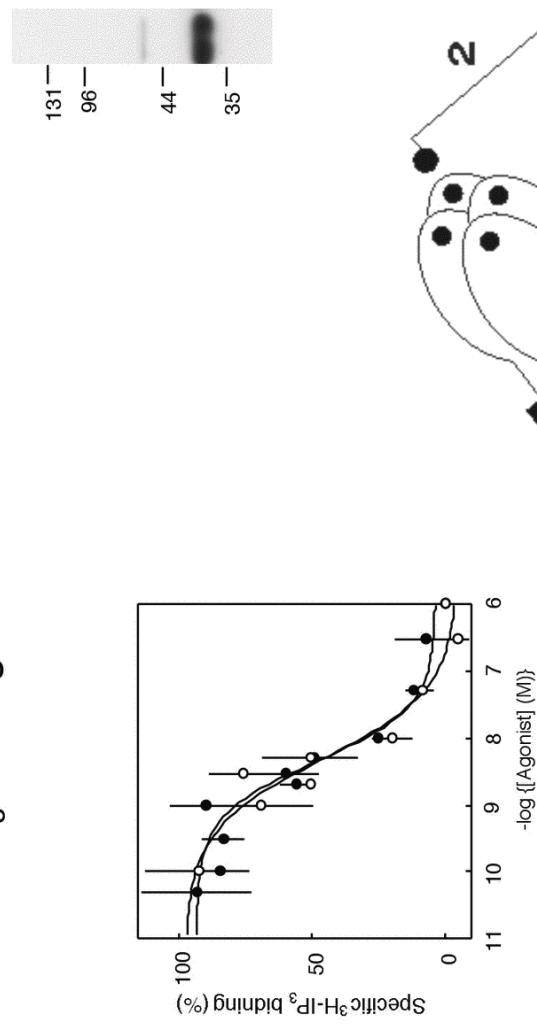
Dimers of IP₃ are more potent in hepatocytes



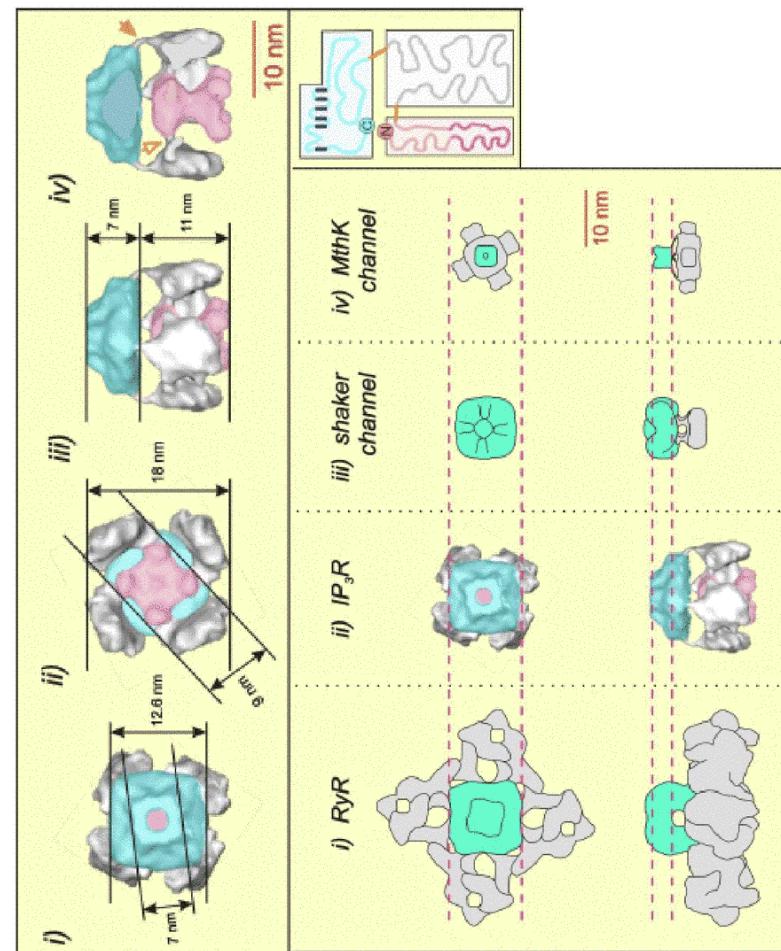
Binding of dimeric IP₃ to cerebellar IP₃ receptors

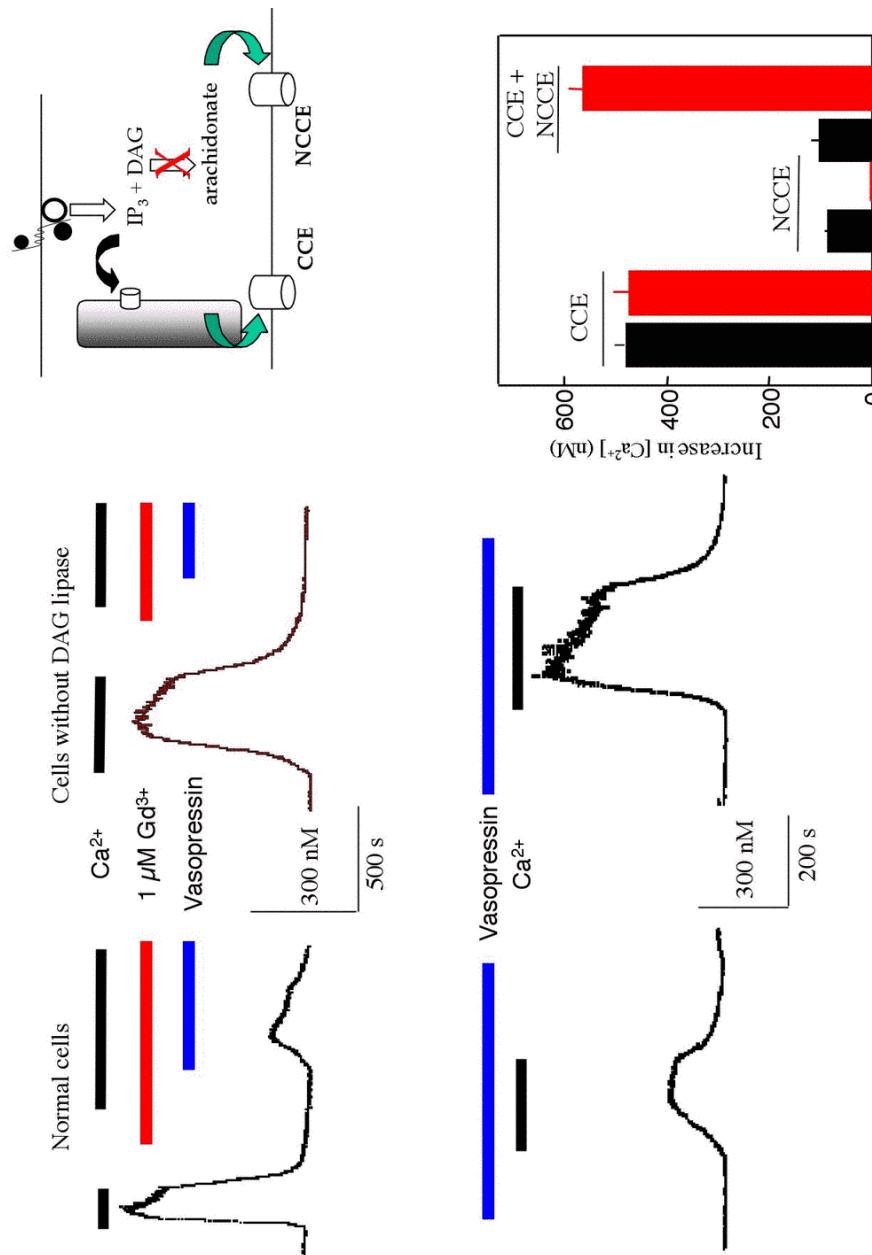


Dimers do not bind with increased affinity
to monomeric IP₃-binding sites

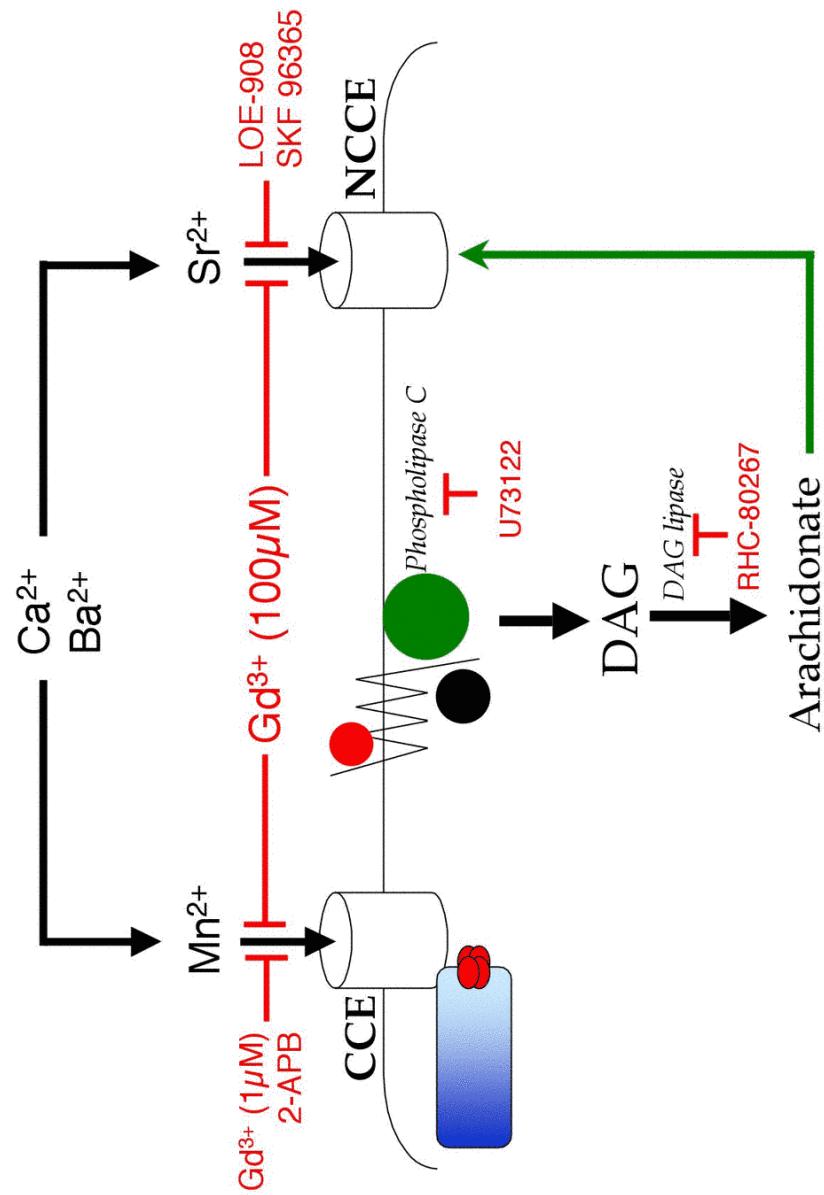


IP₃ probably binds to the central stigma regions

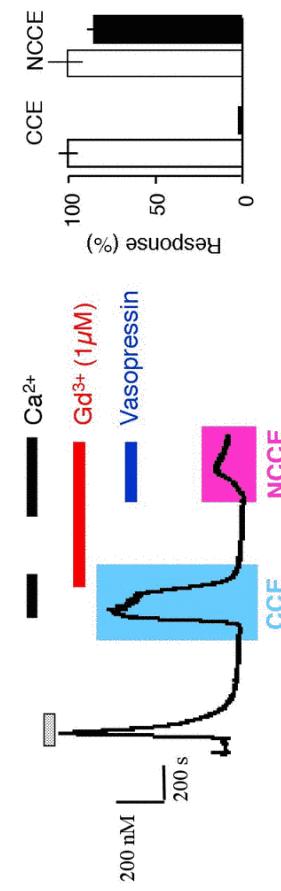




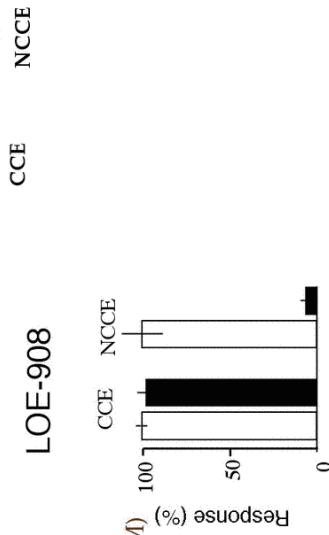
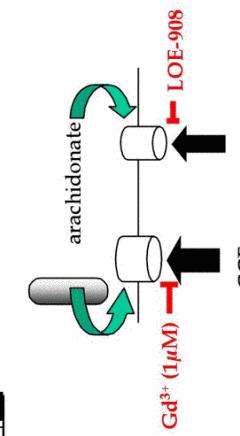
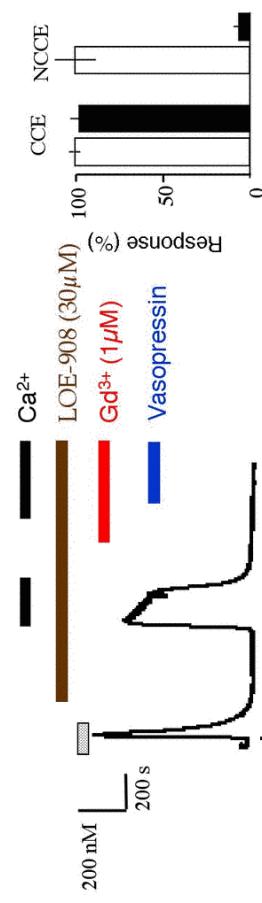
- 2 Ca²⁺ entry pathways, regulated by both limbs of the PI pathway
- Reciprocal regulation of the 2 pathways
- Strict sequence of first NCCE and then CCE activation
- Arachidonic acid and NO mediate activation of NCCE and inhibition of CCE
- Differential activation of NCCE and CCE by different PLC-coupled receptors

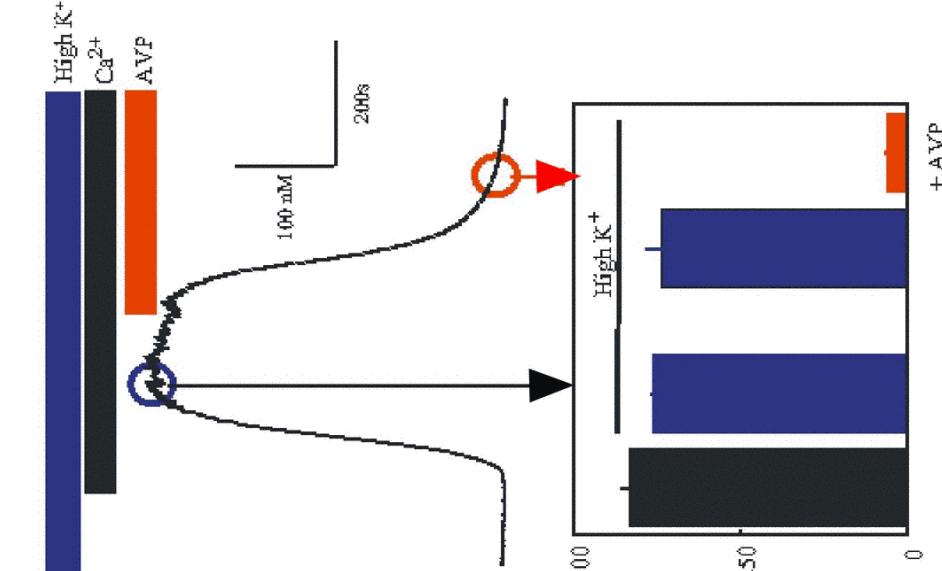
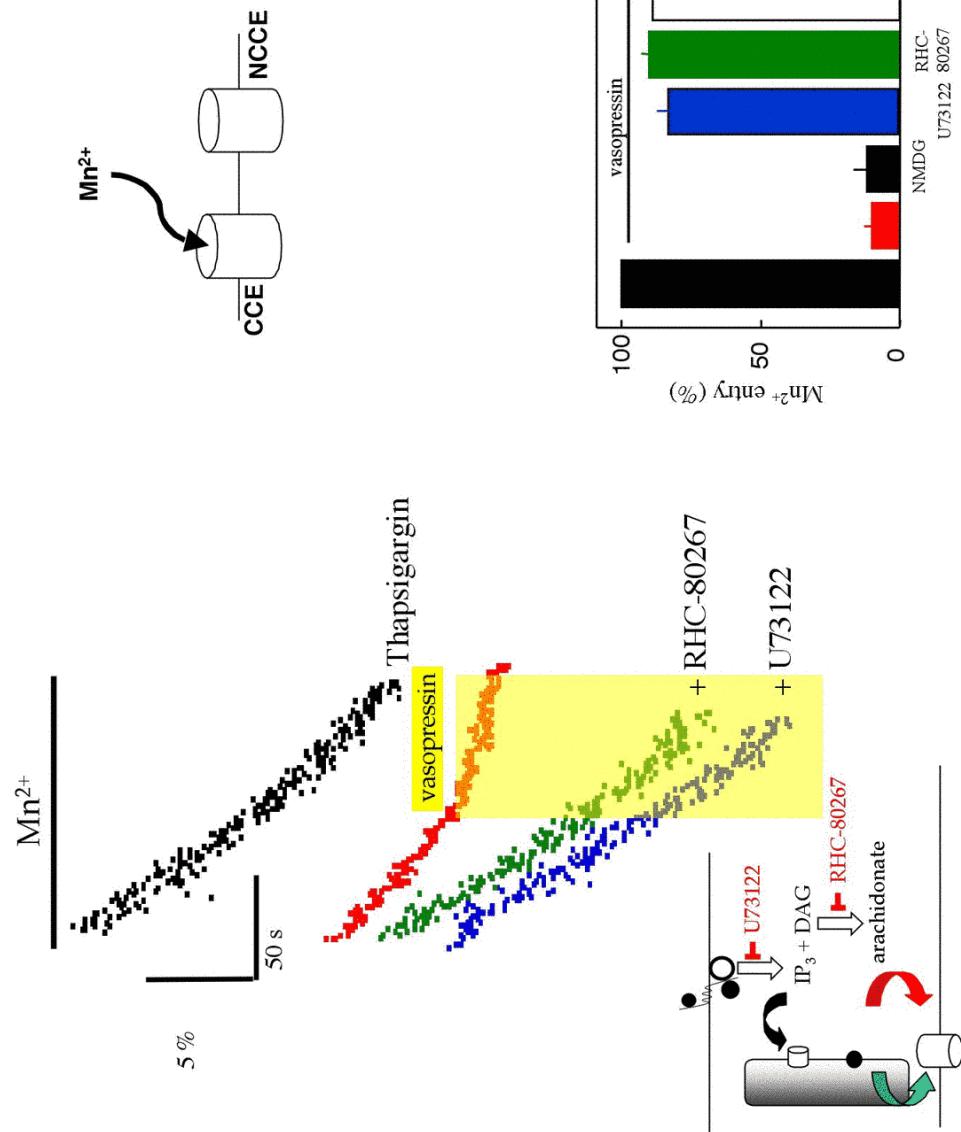


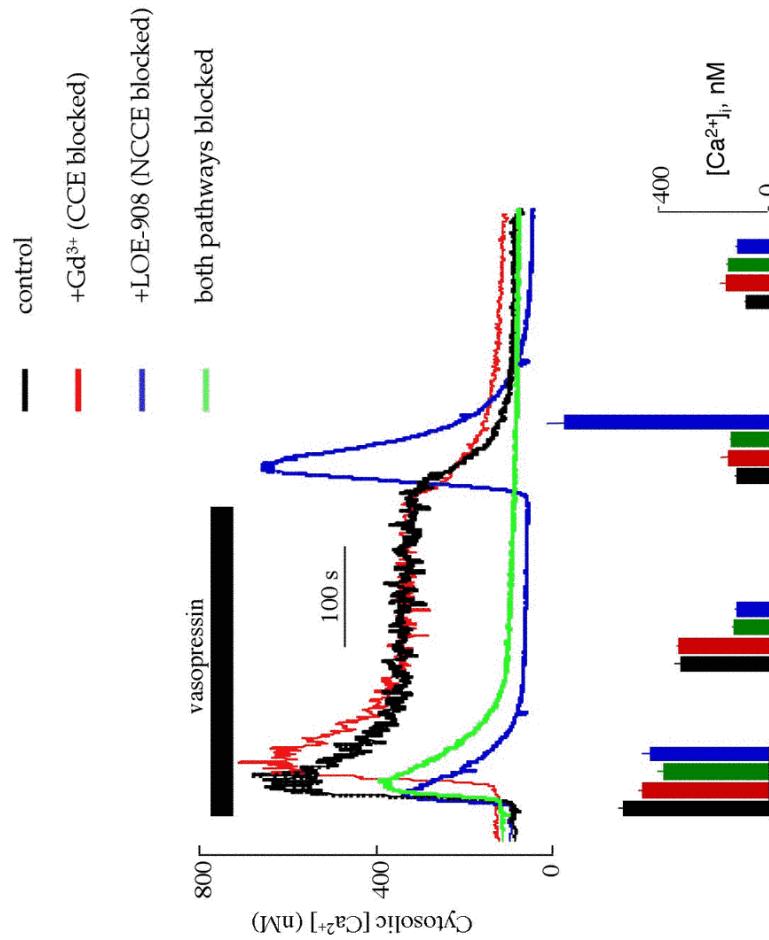
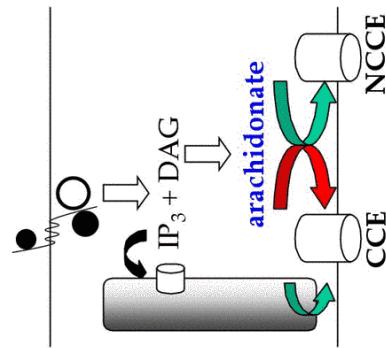
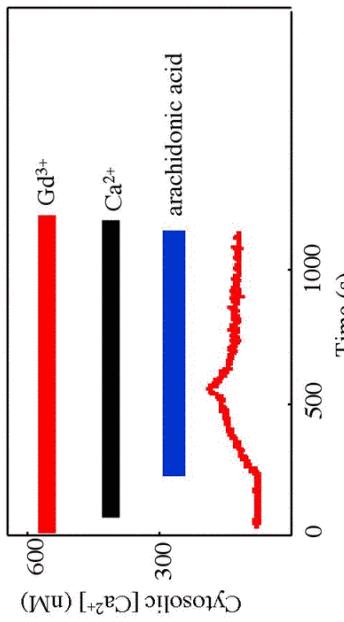
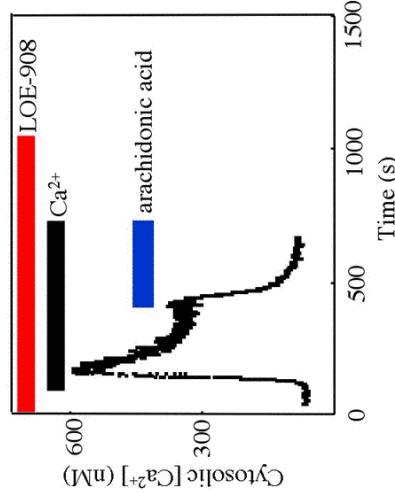
Selective block of CCE

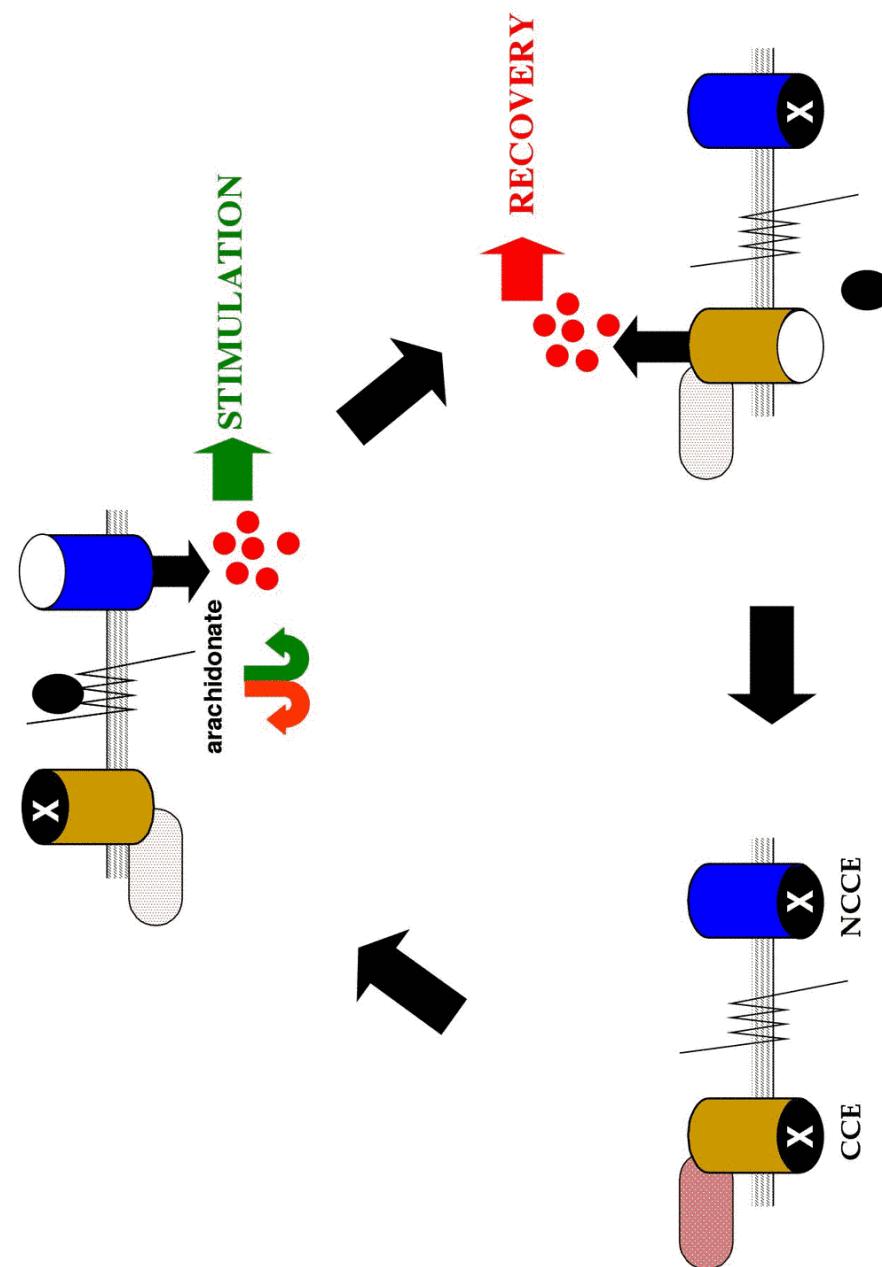
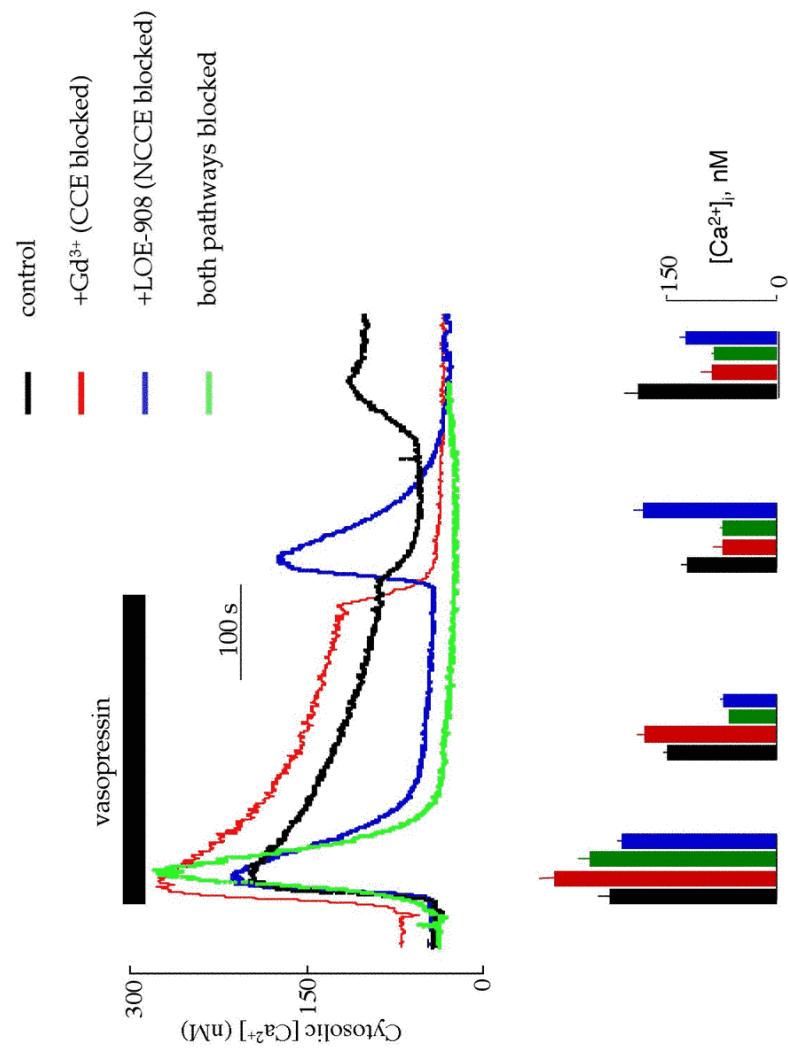


...and selective block of NCCE...

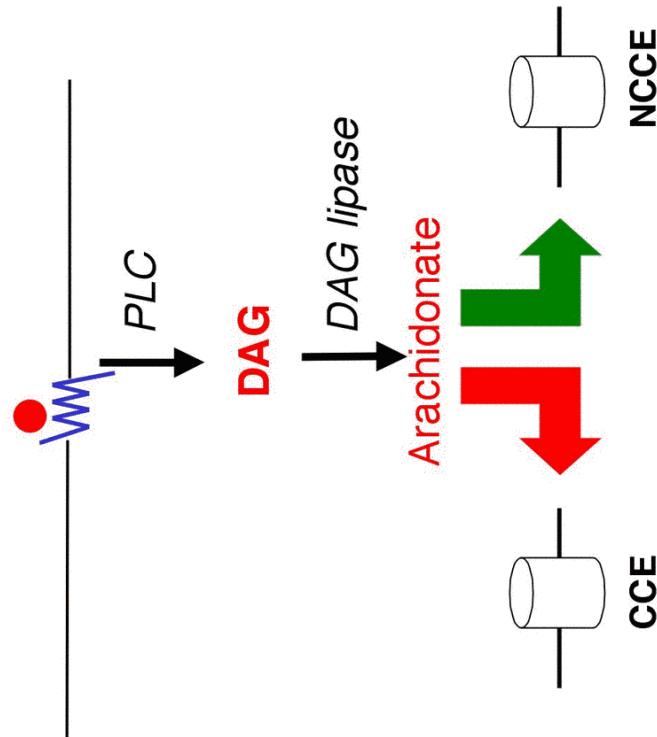




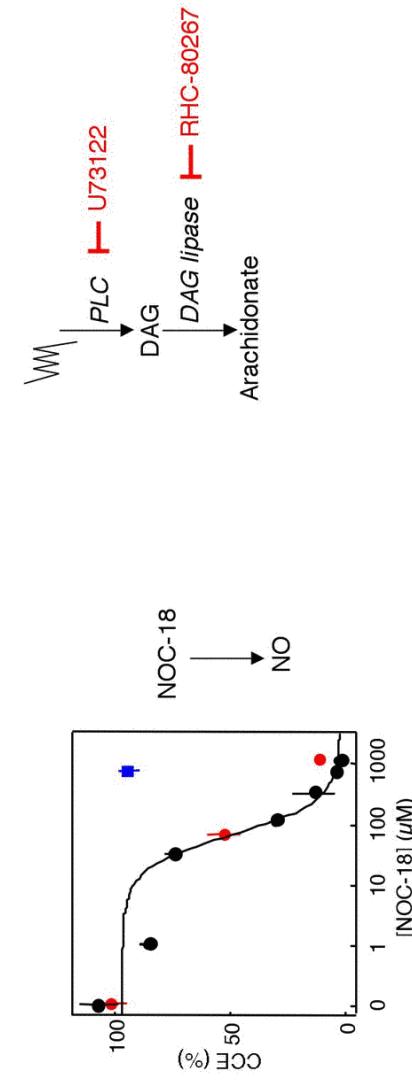
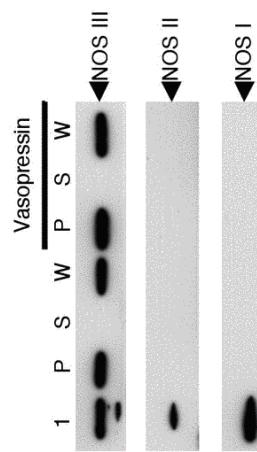
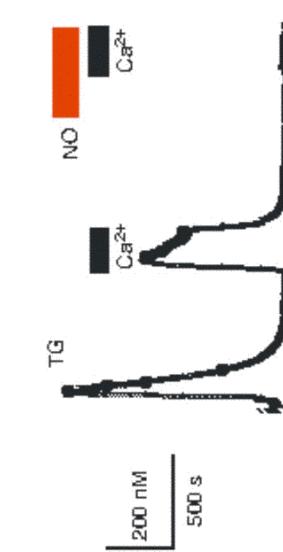
Arachidonate co-ordinates the two Ca²⁺ entry pathways



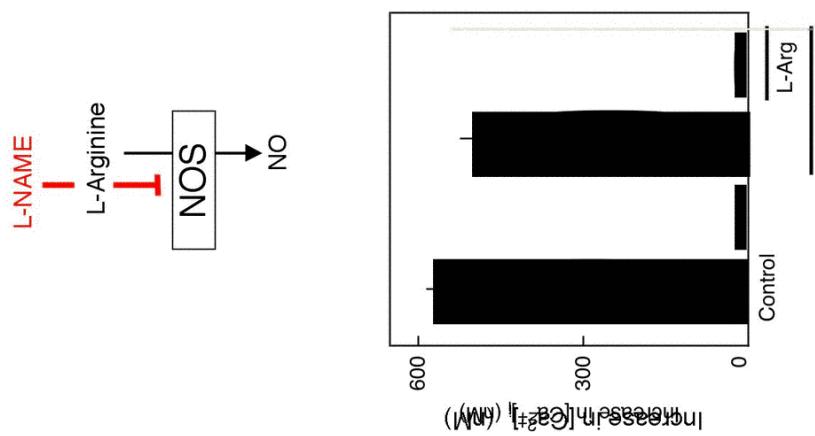
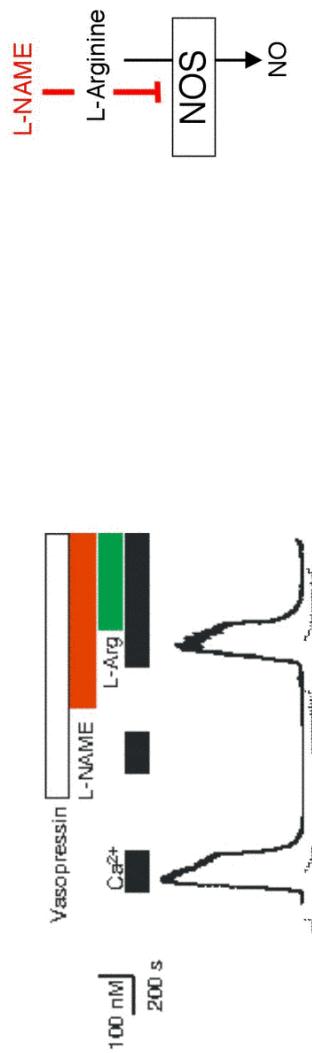
Reciprocal regulation by arachidonate



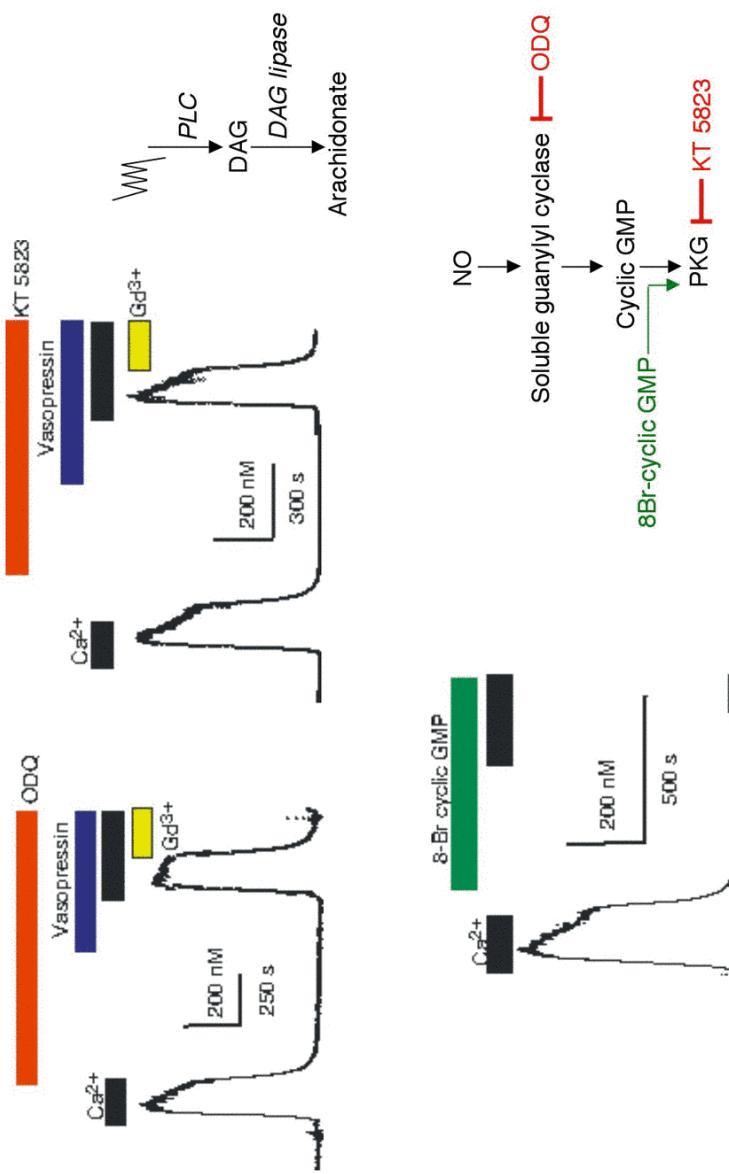
Inhibition of CCE by NO

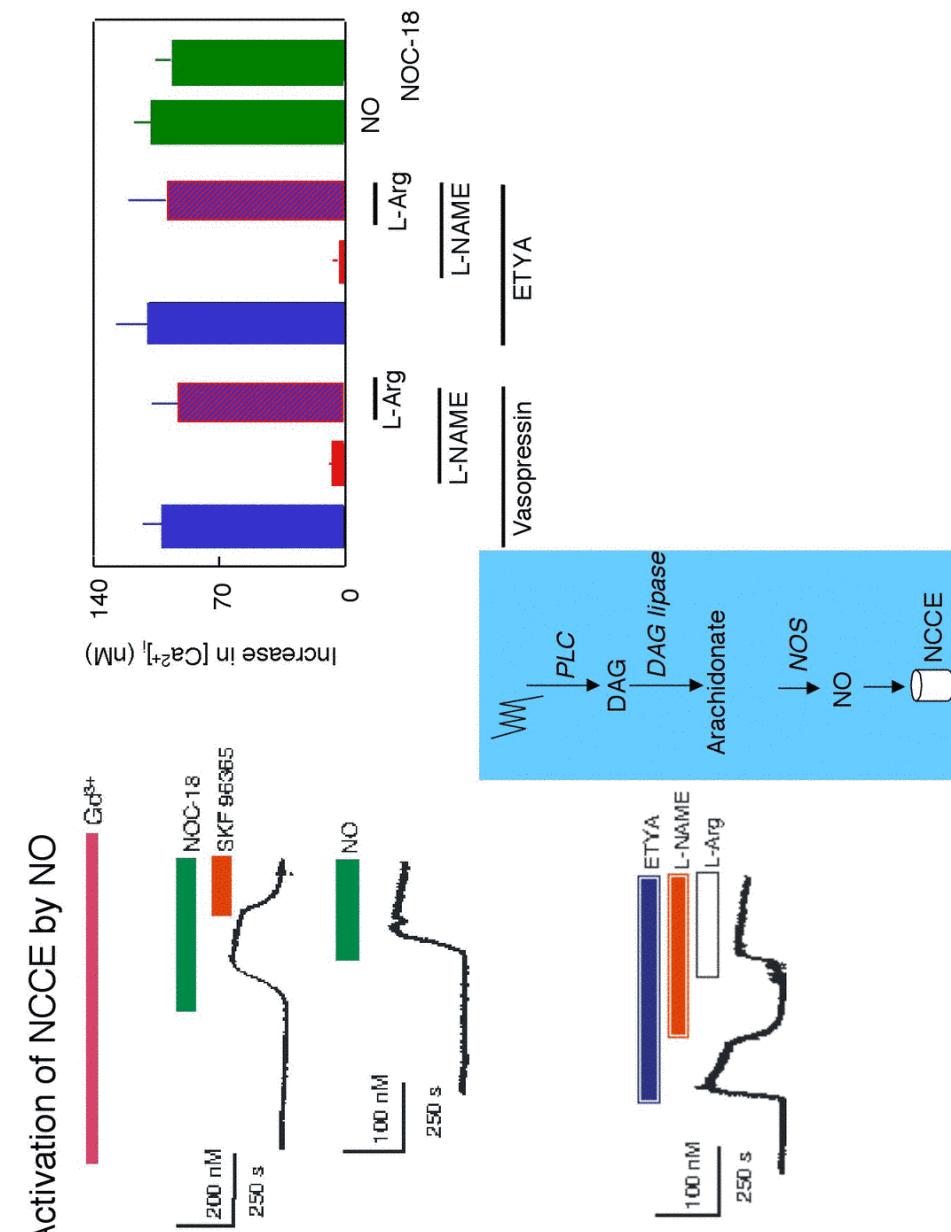
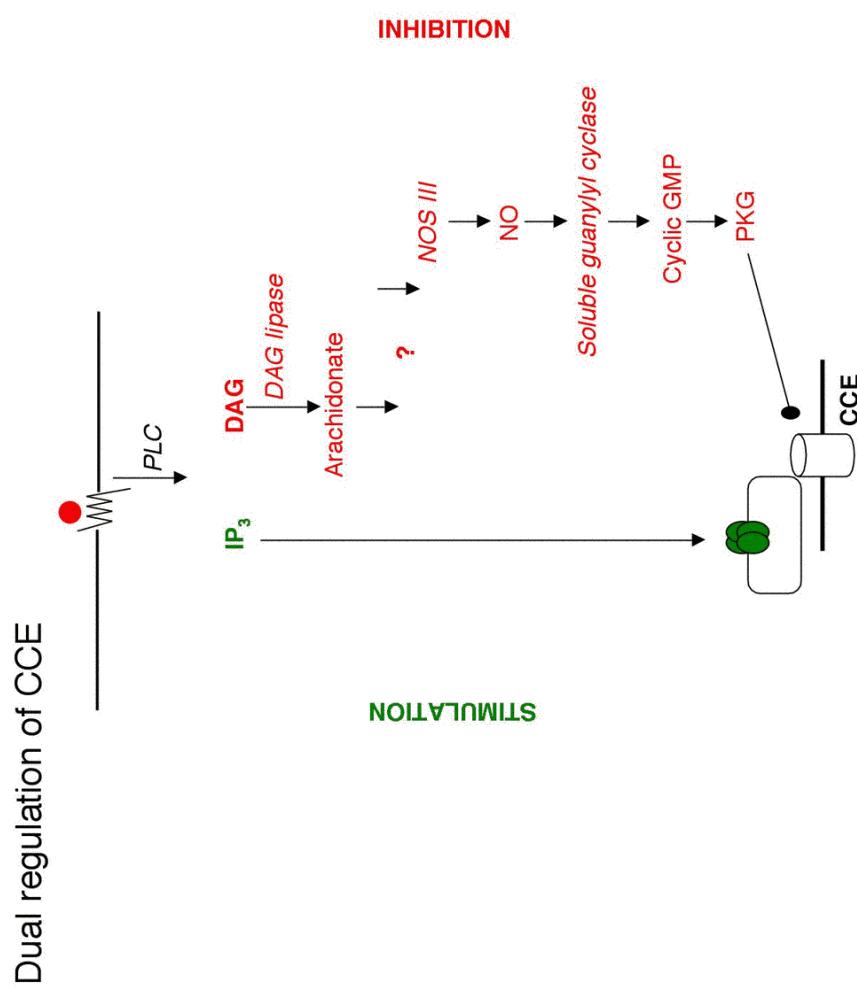


Vasopressin inhibits CCE via NO

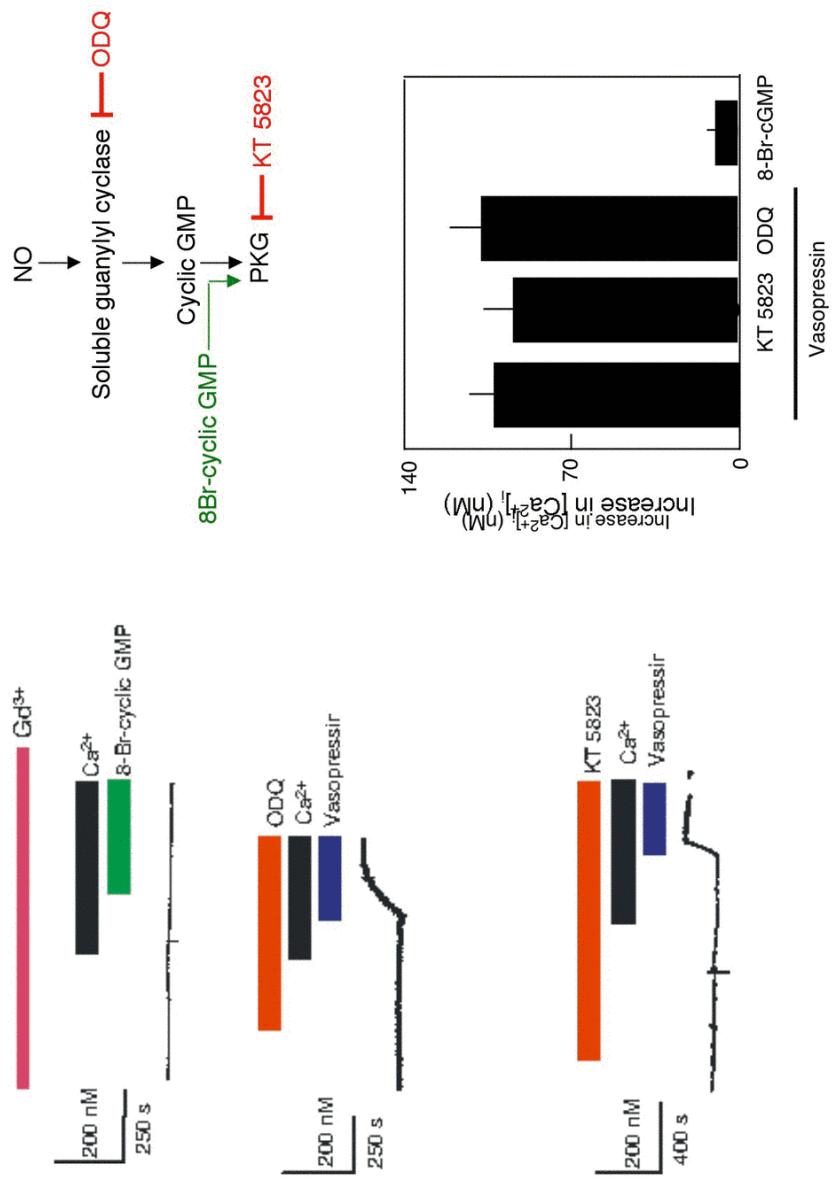


PKG mediates inhibition of CCE by vasopressin

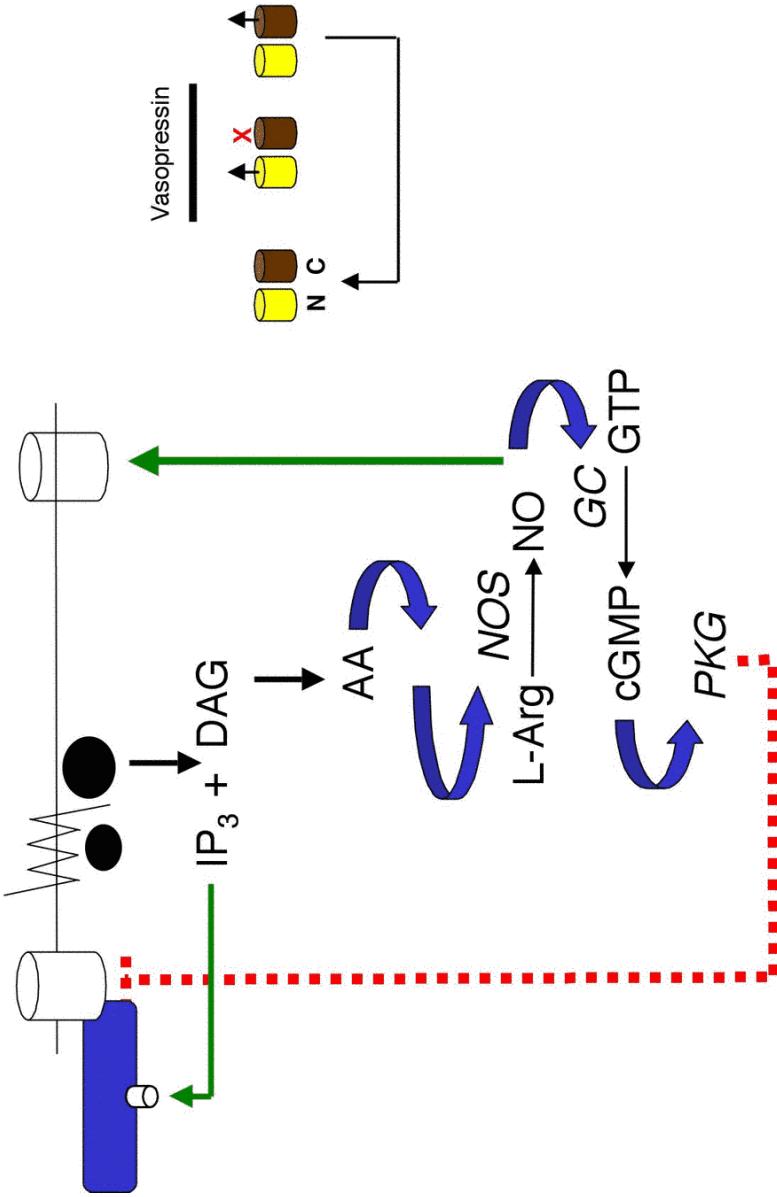




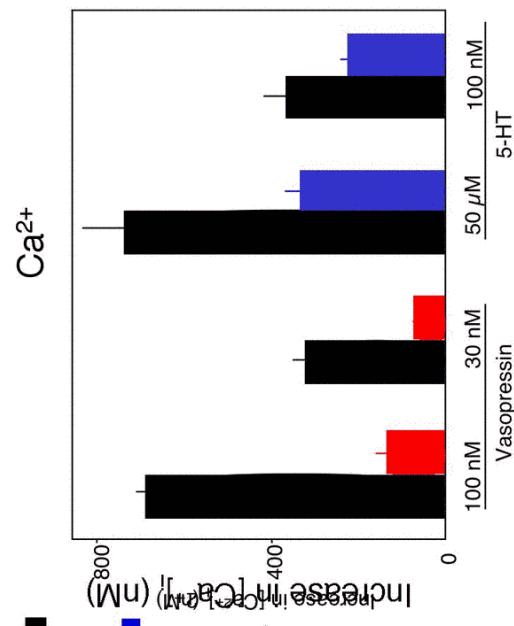
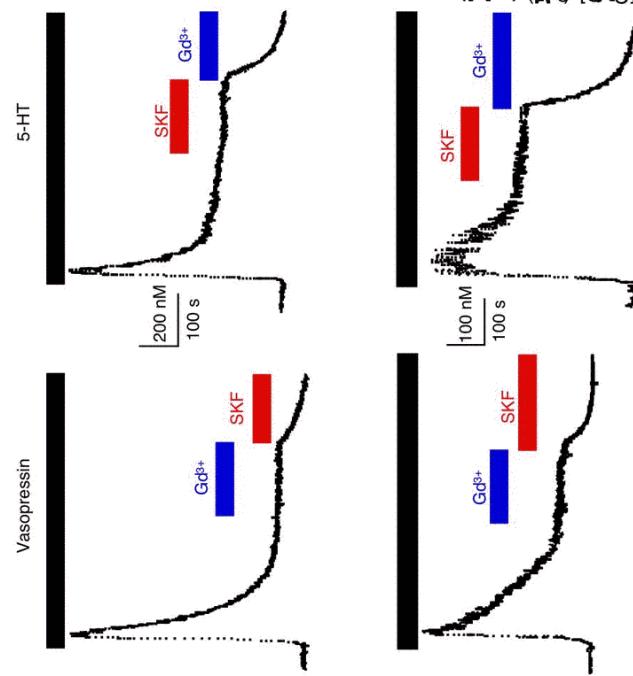
Activation of NCCE does not require PKG



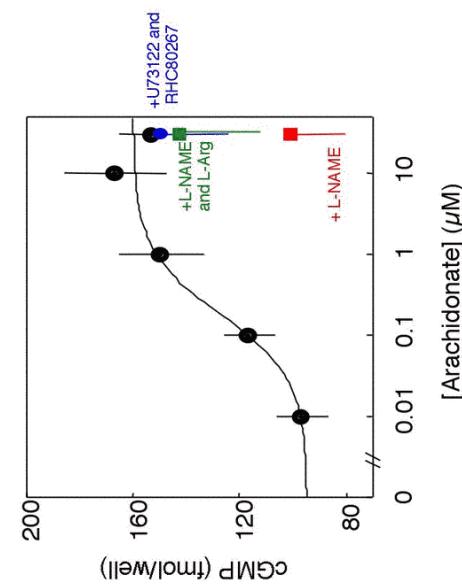
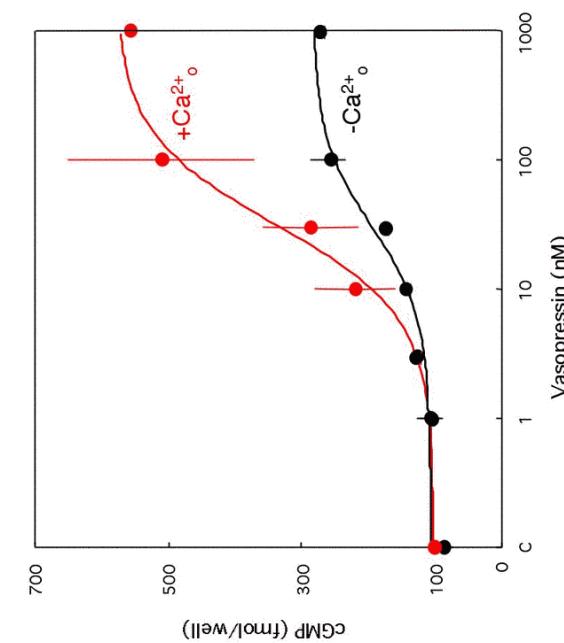
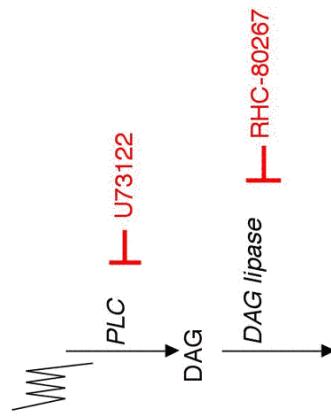
CCE



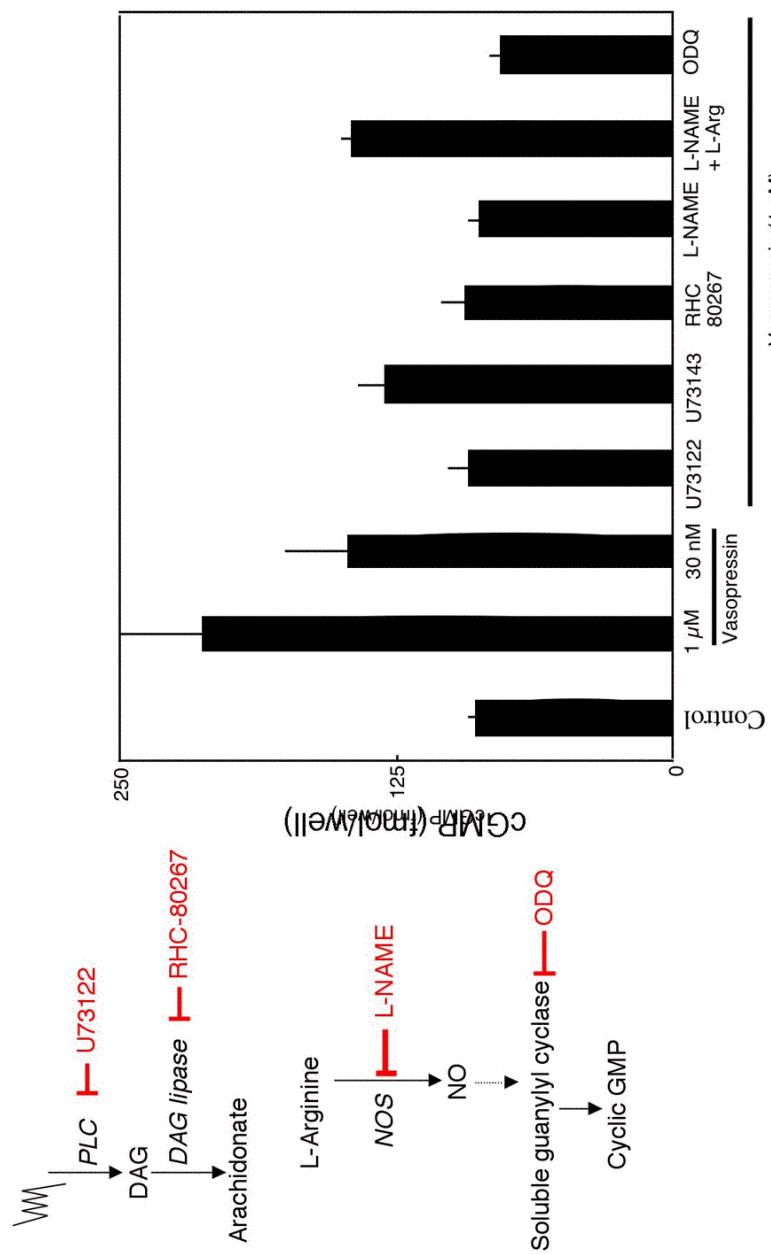
Differential activation of NCCE and CCE by vasopressin and 5-HT



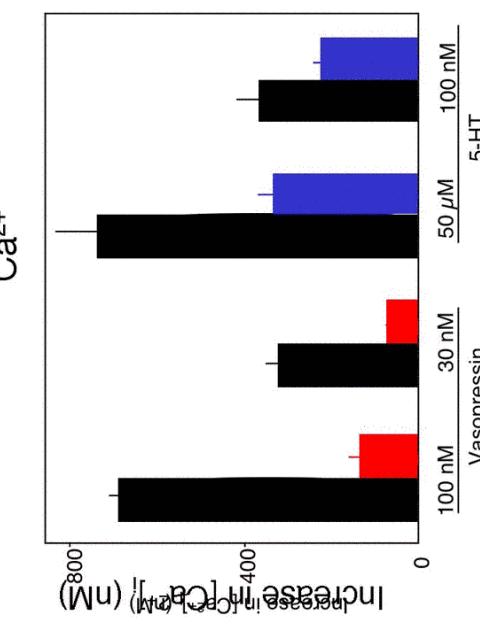
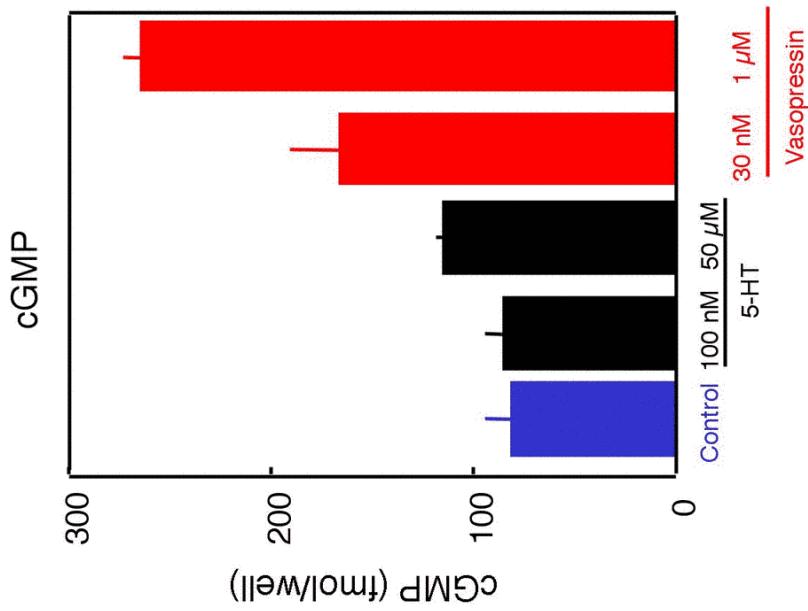
Vasopressin and arachidonate stimulate NOS and cGMP formation

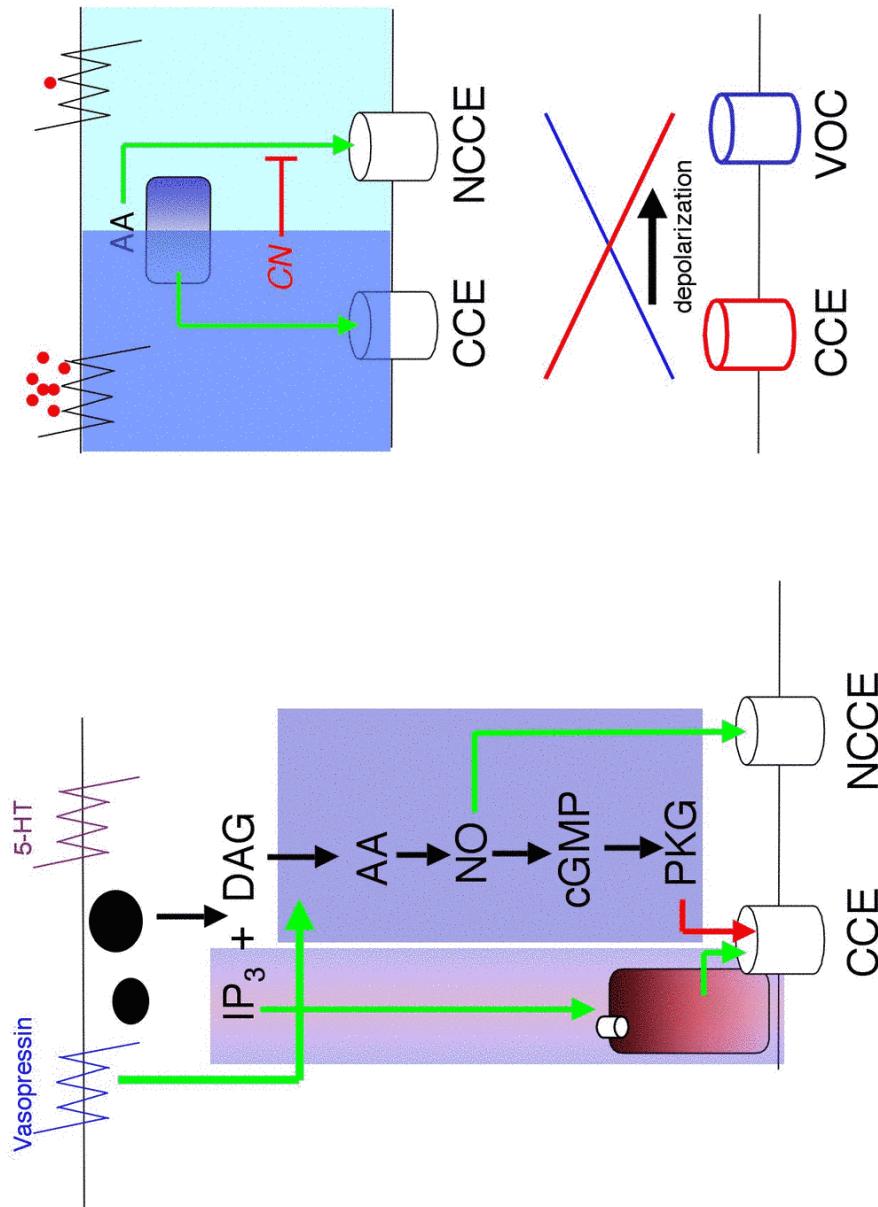


Vasopressin, via arachidonate, stimulates NOS and cGMP formation



Vasopressin, but not 5-HT, stimulates cGMP formation



Co-ordinate regulation of Ca²⁺ entry pathwaysCa²⁺ entry pathways in A7r5 cells

*Ken Byron
Jeanette Dyer
Lisa Broad
Zahid Moneer*

Regulation of IP₃ receptors

Jonathan Merchant

Charles Atkins

Structure of IP₃ receptors

*Pabhashi Fernando
Ed Morris*

Paula da Fonseca

Chemistry

*Stephen Morris
Barry Potter
Andy Riley*

