## IP3R receptors and Ca-induced-Ca release from internal stores

* In the equations:



* NMB and Grp act as an agonist on NMBR and GrpR (q-type GPCRs), initiating IP3 production, leading to a larger Ca release from internal stores. Thus increasing sigh frequency. It is similar to **increasing v1**. *(Li 2016)*
* BIM23042 and RC3095 are antagonists for NMBR and GrpR, respectively. These drugs decrease IP3 production, leasing to less Ca release from internal stores. Thus decreasing sigh frequency. It is like **decreasing v1**. *(Li 2016)*
* Ryanodine, at micromolar concentrations, fully closes ryanodine receptors. Leading to less Ca-induced-ca release from ER. This **might be modeled by decreasing v1**. But since ryanodine receptors are not activated by IP3, it is not totally consistent. Ryanodine with CPA/thapsigargin has been shown to eliminate sighs. *(Toporikova 2015)*

## Ca leak from internal stores

* In the equations:



## SERCA pumps, moving Ca into internal stores

* In the equations:



* CPA or thapsigargin inhibit SERCA (sarco/endoplasmic reticulum Ca ATPase) pumps. Leading to a lack of Ca movement into the ER. This should stop/slow sighs. In the model, this is like **decreasing v3**. (*Toporikova 2015)*

## Tonic Ca uptake (constant uptake)

* In the equations:



* Cadmium blocks Ca channels, and can potentially interfere with Ca uptake into the cytosol. This should **decrease in j0** should decrease sigh frequency. *(Lieske 2000, Toporikova 2015)*

## Activity dependent Ca uptake

* In the equations:



* Cadmium blocks voltage-gated Ca channels. Thus removing Ca influx during bursts of activity. This would be reflected in our model by **decreasing j1**. *(Lieske 2000, Toporikova 2015)*
* Substance P is known to increase eupnea and sigh frequency. In our model, the increase in sigh frequency would be caused by additional Ca influx as a result of the larger and faster eupneic bursts. This could be modeled by **increasing j1**. *(Lieske 2000)*
* Strychnine links a sigh burst more strongly with a preceding burst. This could be due to increased Ca influx during the now larger inspiratory bursts. Modeled by an **increase in j1**. (Borrus 2020 ☺)
* Riluzole slows but does not stop sigh rhythm. This could reflect a decrease in Ca influx as a result of smaller inspiratory bursts. Thus the rhythm slows down as there is less Ca coming in. This would be modeled as a **decrease in j1**. *(Toporikova 2015)*
* Extracellular K+ concentration affects the baseline excitability of neurons. Our lab and others have shown decreasing excitability selectively affects the inspiratory rhythm. But the decrease in inspiratory frequency has a small effect on sigh frequency. This has also been shown for unconventionally high values of K+. *(Toporikova 2015, and us)*

## Ca efflux from cell

* In the equations:

