A Detailed Way to Establish Correlations between Ionic Currents in PD Neurons of the Crab Stomatogastric Ganglion

By LI YU

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And approved by

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Abstract of the Thesis

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Thesis Director: Dr. Jorge Golowasch

Two electrically-coupled PD neurons in the stomatogastric ganglion (STG) of the crab, *Cancer borealis* are coupled with the pacemaker AB neuron. In recent years, several research groups have reported that a number of currents seem to be coexpressed in PD neurons, as revealed by a correlation in the amplitude of the currents, conductances or mRNA that codes for them. Among these currents, the correlations between the transient potassium outward current (I_A), the high-threshold potassium outward current (I_{HTK}) and the hyperpolarization-activated inward current (I_H) are well established. Research also found that some of the currents may be coregulated constitutively, such as I_A-I_H, and some may be dependent on neuromodulators, such as I_A-I_{HTK}, and I_{HTK}-I_H. The study presented here uses a more detailed and different way to measure the maximal conductance of I_A, I_{HTK}, I_H, with the goal of determining if current parameters other than the maximal conductance may be correlated. Here I also analyze possible relationships of the two known components of I_{HTK}: the calcium-dependent potassium current (I_{KCa}) and the delayed rectifier current (I_{Kd}). The results I have observed are consistent with the previous studies and confirm significant positive linear correlations between I_A and I_{HTK}, I_A and I_H, and I_{HTK} and I_H. Even though the sample number is limited, I have also established the correlation between the two components of I_{HTK}: I_{KCa} and I_{Kd}, which is a result that contrasts with those at the mRNA level in which no significant linear correlations between *BK-KCa* (a gene that encodes for I_{KCa}) and *shab* (a gene that encodes for I_{Kd}), and *BK-KCa* and *shaw* (a gene also encodes for I_{Kd}) were found. The other new finding here is the correlation in maximal conductance between I_{KCa} and I_H, and I_{Kd} and I_H, which is consistent with the correlation of *BK-KCa* and *H* (a gene that encodes for I_H), and contrasts with the lack of significant correlations of *shab* and *H*, *shaw* and *H*.

Key Words: HHFit, I_A, I_{HTK}, I_H, I_{KCa}, I_{Kd}, Correlation, PD neurons, STG

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Introduction

The *Crustacean' Stomatogastric Ganglion (STG)*

To maintain a stable neuronal activity is critical in neuronal networks. A well-studied network is the pyloric network of crustaceans, located in STG. The STG is essential for digestion, because instead of orally chewing, crustaceans chew and digest food directly in their stomach and it is the STG that is in charge of the movement of stomach muscles involved in these behaviors. Among the several rhythms that activate the crustacean's digestive system, the gastric and pyloric rhythms are understood best. The STG of crab *C. borealis* is composed of 25-26 neurons (Maynard and Dando, 1974, Kilman and Marder, 1996) which form central pattern generators (CPGs) (Selverston and Moulins, 1985, Getting, 1989). These CPGs generate different rhythmic motor patterns. The crab pyloric CPG rhythm is more fully characterized than the gastric rhythm. The time period of the pyloric rhythm is approximately 1s which is much faster than the gastric rhythm (5-10s) (Weimann et al., 1991). There are one anterior burster neuron (AB), two pyloric dilator neurons (PD), one ventricular dilator neuron (VD), one inferior cardiac neuron (IC), one lateral pyloric neuron (LP) and three to five pyloric neurons (PY). The network between all these neurons establishes the pyloric rhythm circuitry (Figure1). The AB neuron serves as a pacemaker in this circuit. The PD neurons, which are electrically coupled with the pacemaker AB neuron, fire with AB and help to shape the rhythm. The rhythm activity is dependent on the neuromodulators released from neurons in the adjacent ganglia which project into the STG (Luther et al., 2003). AB/PD neurons strongly inhibit the other cells in this network. The LP neuron is the first neuron to recover from the inhibition and its firing causes the valve to the pyloric region to

close. IC cell fires in phase with LP cell and help to control the valve. The LP neuron also inhibits the AB/PD neurons which prevents them from firing again. In the final phase of the cycle, PY neurons recover from the inhibition and begin firing. These neurons control the pyloric muscles that are responsible for moving the sieve plates in the pylorus that sort out the food for further digestion. VD cell often fires in phase with the PY cells, but its firing is complex and not easily correlated to just one movement.

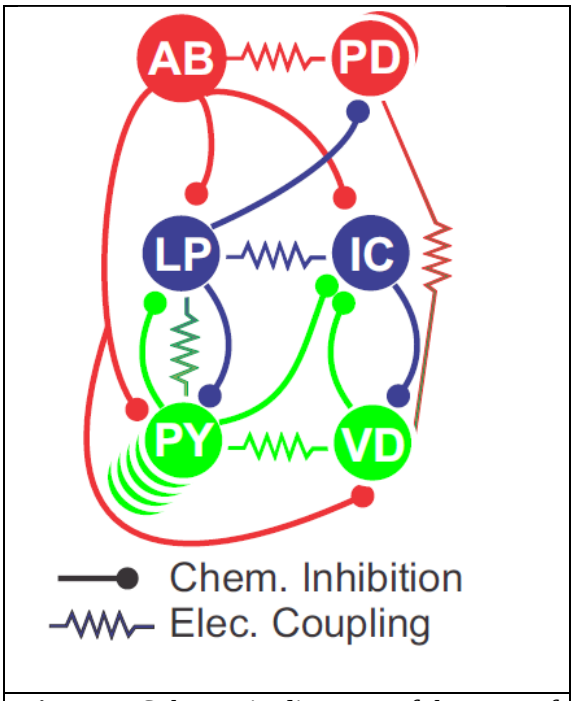


Figure 1.*Schematic diagram of the core of pyloric network in crab STG.*

Correlations between I_A, I_{HTK}, I_H

To maintain stable oscillatory activity it has been hypothesized that the ionic currents involved must maintain an approximately constant level relative to each other from different neurons. This is observed as linear correlations between ionic currents or their maximal conductances (McAnelly and Zakon, 2000, MacLean et al., 2003, Khorkova and Golowasch, 2007, Temporal et al., 2012). Correlations of ionic currents could maintain neuronal stability.

A-type potassium channels have been observed to be important in determining neuronal activity during pyloric cycle (Graubard and Hartline, 1991, Tierney and Harris-Warrick, 1992, Baro et al., 1997). There are two key factors to regulate this, one is neuronal directly to regulate activity, often homeostatically (Desai et al., 1999, Cudmore and Turrigiano, 2004, Loebrich and Nedivi, 2009),and neuromodulators modify the expression of ionic channels by regulating the expression levels or properties of the channels (MacLean et al., 2003, MacLean et al., 2005, Khorkova and Golowasch, 2007). The correlation between I_A and I_{HTK} in PD neurons is neuromodulator dependent, not activity-dependent. In decentralized preparations, where neuromodulators are removed, the correlation between I_A and I_{HTK} amplitude is lost. But by adding picrotoxin, neuromodulator released naturally, the correlations between I_A and I_{HTK} is rescued (Temporal et al., 2012).

Coregulation of gene expression vs. Correlation of ionic channel expression

Baro et al. (1997) showed that I_A was encoded by the *shal* K^+ channel gene in the pyloric network of spiny lobster (Baro et al., 1997). MacLean and colleagues reported that microinjection of *shal* gene RNA increases I_A as well as I_H in activity-independent fashion (MacLean et al., 2003). In order to detect the exact role of I_A in pyloric network activity, they conducted another study in 2005 (MacLean et al., 2005). They microinjected RNA for a *shal*-GFP fusion protein into PD, LP, VD and IC neurons. In all four neuron types, there was a similar increase in I_A amplitude. The translation of *shal* RNA has almost the same efficiency in those four neuron types. As before, there were concomitant increase of I_H in all pyloric neurons. The interesting finding was that

the cell firing properties changed modestly in all neuron types, even though there were significant increase in I_A and I_H. They set up two models to examine why the normal firing properties were unchanged even though there were large changes in ionic currents. One tested the mislocalization of the *shal* protein. They observed that overexpression of the *shal* protein was only found in soma and initial neurite, which was different from the normal distribution of the *shal* gene product in non-injected neurons. By using a three-compartment mathematical model, they tried to examine if the mislocalization of the *shal* gene expression could fully explain the phenomenon described above. The results showed that the mislocalization alone could only partially explain the failure of the changing of neuronal firing properties. So they developed a second model that was based on a compensatory interaction between I_A and I_H. Their studies supported the hypothesis that homeostatic upregulation of I_H could compensate for the upregulation of I_A over a wide range of currents levels in all pyloric neurons. MacLean and colleagues also examined the correlation between the *shal* and the *H* in mRNA levels. They reported a positive coregulation between them and this coregulation was natural instead of the result of an experimental artifact. *shal* gene and *H* gene may be coregulated along the way of transcription, translation and after translation, and may be reflected in the correlated expression of their currents. New studies in crab STG neurons have also reported that the relation between I_A and I_H is intrinsic, not activity-dependent (Schulz et al., 2006, Khorkova and Golowasch, 2007, Schulz et al., 2007, Temporal et al., 2012). Temporal et al. (2012) found that I_{HTK}, I_A and I_H are all correlated at the maximal conductance levels in both PD neurons and LP neurons. When they removed neuromodulatory input, they found that correlations are cell-type specific. In PD neurons, the loss of neuromodulator input disrupted the correlations between g_A and

g_{HTK}, and g_H and g_{HTK}. The correlation between g_H and g_A was not affected but the slope significant increased. In LP neurons, all correlations remain, but the slopes decreased. At the mRNA levels, PD neurons express these three mRNA species in a three-way correlated manner, whereas LP neurons appear to do so only for the pairs *shal* vs. *H* and *BK-KCa* vs. *H* and not for the *BK-KCa* vs. *shal* pair. They found that neuromodulators can have distinct and independent effects on, and perhaps independent pathways for, regulation of transcription, translation and posttranslational mechanisms involved in generating membrane currents. They revealed important differences in how a correlated expression of ionic currents ultimately comes about, suggesting multiple levels of potential regulation: along the way from transcription, translation and post-translation.

The purpose of this study

Based on Hudgkin-Huxley equations, ionic currents, such as I_A, I_{HTK} and I_H, are characterized by several parameters, for instance, maximal conductances, activations parameters, and inactivation parameters. HHfit is a customer developed software that was used to fit ionic currents of crab PD neurons using Hudgkin-Huxley equations. With the information of current parameters, I hypothesize that correlations may exist between other parameters in addition to between maximal conductances.

Based on reports of correlations between *shal* and *BK-KCa*, and *H* and *BK-KCa* in PD neurons and lack of correlations between *shal* and *shab*, *shal* and *shaw*, *H* and *shal*, *H* and *shaw*, and *BK-KCa* and *shal*/*shaw* (Schulz et al., 2007), I hypothesize that correlations may exist between I_A and I_{KCa}, I_H and I_{KCa} in maximal conductance, but be lacking between I_A and I_{Kd}, I_H and I_{Kd}, and I_{KCa} and I_{Kd}. Here I_{HTK} was

pharmacologically separated into its two known components: I_{KCa} and I_{Kd} in order to test this hypothesis.

Materials and Methods

Electrophysiology

The data were obtained from Dr. Shunbing Zhao's experiments from 2009 to 2012. All data involved in this study are from PD neurons in the crab *C. borealis*. From two-electrode voltage clamp electrophysiological recordings Dr. Zhao measured I_A, I_{HTK}, I_H in normal saline (Golowasch and Marder, 1992, Khorkova and Golowasch, 2007, Zhao and Golowasch, 2012).Since I_A is inactivated at voltage $\geqslant$-40mV and I_{HTK} is activated by depolarization from a holding voltage -40mV, I_{HTK} is measured using this protocol without I_A contamination. But I_{HTK} here is non-leak subtracted. I_A is completely inactivated at -80mV. So by subtracting the total outward current measured by depolarization from a holding voltage -40mV from the current measured in the same condition but from a holding voltage -80mV, we can determine I_A. I_H is an inward current measured with hyperpolarizing voltage steps from a holding voltage of -40mV. IHTK was pharmacologically separated into its two components: IKCa and IKd. Using the IHTK measurement protocol in the presence of Mn2+ (in exchange for Ca2+), which is a drug used to block the inward calcium current ICa and indirectly IKCa. The remaining currents using the same protocol as for IHTK but in Mn2+ saline are IKd + Ileak. Leak current is a linear current. IKCa is separated by subtracting the total outward potassium current in Mn2+ saline from the current measured in the same way in normal saline.

Data analysis

I use the software Clampfit 10.3 to select 6 traces from each identified current. These

traces are then used by the custom developed software HHFit. HHfit is a manual fitting software which is based on Hodgkin-Huxley-type equations to fit a current measured in voltage-clamp. The Hodgkin-Huxley equation is:

$$I_x(V) = g_x m^p(V) h^q(V)(V - E_x) \qquad \textbf{(Eq. 1)}$$

g_x is the maximal conductance, $m_x(V)$ is the activation term, $h_x(V)$ is inactivation term, V is the voltage, E_x is the reverse potential of the ion carried by current *x*.

$$m_\infty(V) = \frac{1}{1 + \exp(-(V - V_m)/K_m)} \qquad \textbf{(Eq. 2)}$$

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \qquad \textbf{(Eq. 3)}$$

$$\tau_m(V) = T_{m-low} + \frac{T_{m-hi} - T_{m-low}}{1 + \exp(-(V - V_m)/K_m)} \qquad \textbf{(Eq. 4)}$$

$h_x(V)$ has the same form as $m_x(V)$ shown in equation 2, 3, 4. Sometimes a current can only be properly fit with two current terms similar to Eq. 1 (see below).

Hodgkin-Huxley equation for I_A

$$I_A(V) = g_{A1} m_{A1}(V) h_{A1}(V)(V - E_A) + g_{A2} m_{A2}(V)(V - E_A) \qquad \textbf{(Eq. 5)}$$

The holding voltage for I_A is -80mV, and we assume the current is carried only by K^+ (Golowasch and Marder, 1992). We also assume that E_A = -80mV. g_{A1} is the maximal conductance of a fast transient component, while g_{A2} is the maximal conductance of a inactivating component.

Hodgkin-Huxley equation for I_{HTK}

$$I_{HTK}(V) = g_{leak}(V - E_{leak}) + g_{HTK1}m_{HTK1}(V)h_{HTK1}(V)(V - E_K) + g_{HTK2}m_{HTK2}(V)(V - E_K)$$

(**Eq. 6**)

The holding voltage for I_{HTK} is -40mV, and we assume the current is carried only by K^+ (Golowasch and Marder, 1992), with E_{HTK} = -80mV. I_{HTK} is not leak subtracted, so it is composed of I_{leak} plus two K^+ current components. g_{HTK1} is the maximal conductance of the transient component and g_{HTK2} is the maximal conductance of the steady state component.

When I_{HTK} is separated into I_{KCa} and I_{Kd}, I_{KCa} is still composed of two component, one transient and one steady state:

Hodgkin-Huxley equation for I_{KCa}

$$I_{KCa}(V) = g_{KCa1}m_{KCa1}(V)h_{KCa1}(V)(V - E_K) + g_{KCa2}m_{KCa2}(V)(V - E_K) \qquad (\textbf{Eq. 7})$$

The holding voltage for I_{KCa} is -40mV. g_{KCa1} is the maximal conductance of the transient component of I_{KCa}, while g_{KCa2} is the maximal conductance of the steady state component of I_{KCa}.

Hodgkin-Huxley equation for I_{Kd}

$$I_{Kd}(V) = g_{leak}(V - E_{leak}) + g_{Kd}m_{Kd}(V)(V - E_K) \qquad (\textbf{Eq. 8})$$

I_{Kd} is contaminated by the leak current, and it only has an activation term. The holding voltage is -40mV and E_{Kd} = -80mV.

Hodgkin-Huxley equation for I_H

$$I_H(V) = g_{leak}(V - E_{leak}) + g_H m_H(V)(V - E_H) \qquad \text{(Eq. 9)}$$

I_H here is also a current with leak contamination and only has an activation term.

The holding voltage is -40mV, we assume E_H= -15mV.

Three examples of fitting I_A, I_{HTK} and I_H are shown, respectively in Figure 2.

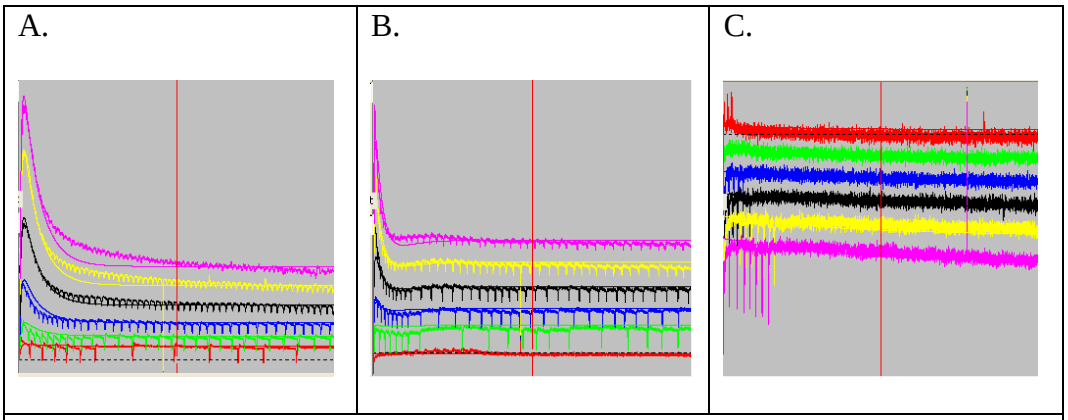


Figure 2. *Fitting of Ionic currents*. The thin lines correspond to fits with the respective Hudgkin-Huxley equations of the raw currents shown. **A**, Fitting example for I_A by using Eq 5. Red: -40.3mV; Green: -30.4mV; Blue: -20.6mV; Black: -10.8mV; Yellow: -1.2mV; Purple: 7.2mV. **B**, Fitting example for I_{HTK} using Eq. 6. Red: -60.0mV; Green:-30.2mV; Blue: -20.4mV; Black: -10.6mV; Yellow: -0.9mV; Purple: 8.9mV. **C**, Fitting example for I_H using Eq. 9. Red: -60.4mV; Green: -70.4mV; Blue: --80.4mV; Black: -90.4mV; Yellow: -100.4mV; Purple: -110.4mV.

Statistical Analysis

Origin 8 was used for graphing and statistical analysis. As reported, the statistical significance means the significance value $p<0.05$ is significant and $p<0.001$ is highly significant.

Results

The relation between the activation and inactivation of transient potassium outward current I_A

There are two stages of I_A, one is activation, the other is inactivation (See Eq.5). Several groups have characterized the kinetics of activation and inactivation of I_A (Cuello et al., 2010), as well as the role of I_A on the electrical properties of neurons in different animal systems (Golowasch and Marder, 1992, Tierney and Harris-Warrick, 1992, Zhao and Golowasch, 2012).

In LP neurons, I_A has a strong dependence on voltage and time during the activation and inactivation processes (Golowasch and Marder, 1992). At -40mV, I_A begins to activate, and the activation increases steeply above -40mV to around +20 mV. After +20mV, the activation stops increasing. Studies from previous groups reported that the voltage dependence of I_A activation is fit very well by a sigmoidal function of voltage (Connor and Stevens, 1971, Neher, 1971, Cobbett et al., 1989, Golowasch and Marder, 1992).

The activation of I_A is much faster than its inactivation. At -90mV or more negative, I_A is de-inactivated, and when the voltage becomes more positive, I_A starts to inactivate. It is completely inactivated when the voltage reaches -40mV or higher. Like activation, the inactivation of I_A can also be fit by a sigmoidal function of voltage (Connor and Stevens, 1971, Neher, 1971, Cobbett et al., 1989, Golowasch and Marder, 1992). And there may exists an intrinsic relation between them as shown before (Connor and Stevens, 1971, Neher, 1971, Cobbett et al., 1989, Cuello et al., 2010). By using HHfit,

g_{A1} and g_{A2} were determined (see Eq. 5). Comparing these two parameters, a strong positive linear correlation between them is observed (Figure 3), as expected if both terms correspond to the activity of the same channels.

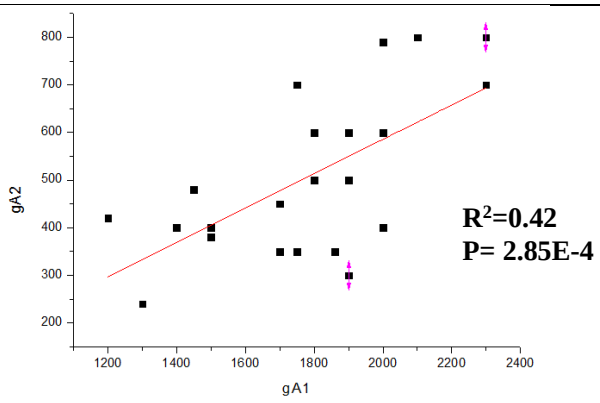


Figure 3. *Correlations between two components of I_A.* Points correspond to g_{A1} and g_{A2} from 25 different PD cells. The correlation is highly significant. Ionic conductances are reported in nS.

The relation between two outward currents: I_A vs. I_{HTK}

Khorkova and Golowasch reported that I_A and I_{HTK} were correlated in PD neurons of the crab STG(Khorkova and Golowasch, 2007).

In the Temporal et al. study, they examined correlations between I_A, I_{HTK} and I_H in PD and LP neuron of crab STG (Temporal et al., 2012). They reported that the correlation between I_A and I_{HTK} at the mRNA level is cell type specific, while the correlation between them appears to be non-cell type specific.

Consistent these with previous studies, our results show a significant positive linear correlation between g_A and g_{HTK} in PD neurons. In fact, all four combinations (g_{A1} vs. g_{HTK1}; g_{A1} vs. g_{HTK2}; g_{A2} vs. g_{HTK1}; g_{A2} vs. g_{HTK2}) (See Equations 5, 6) show each linear correlations (Figure 4).

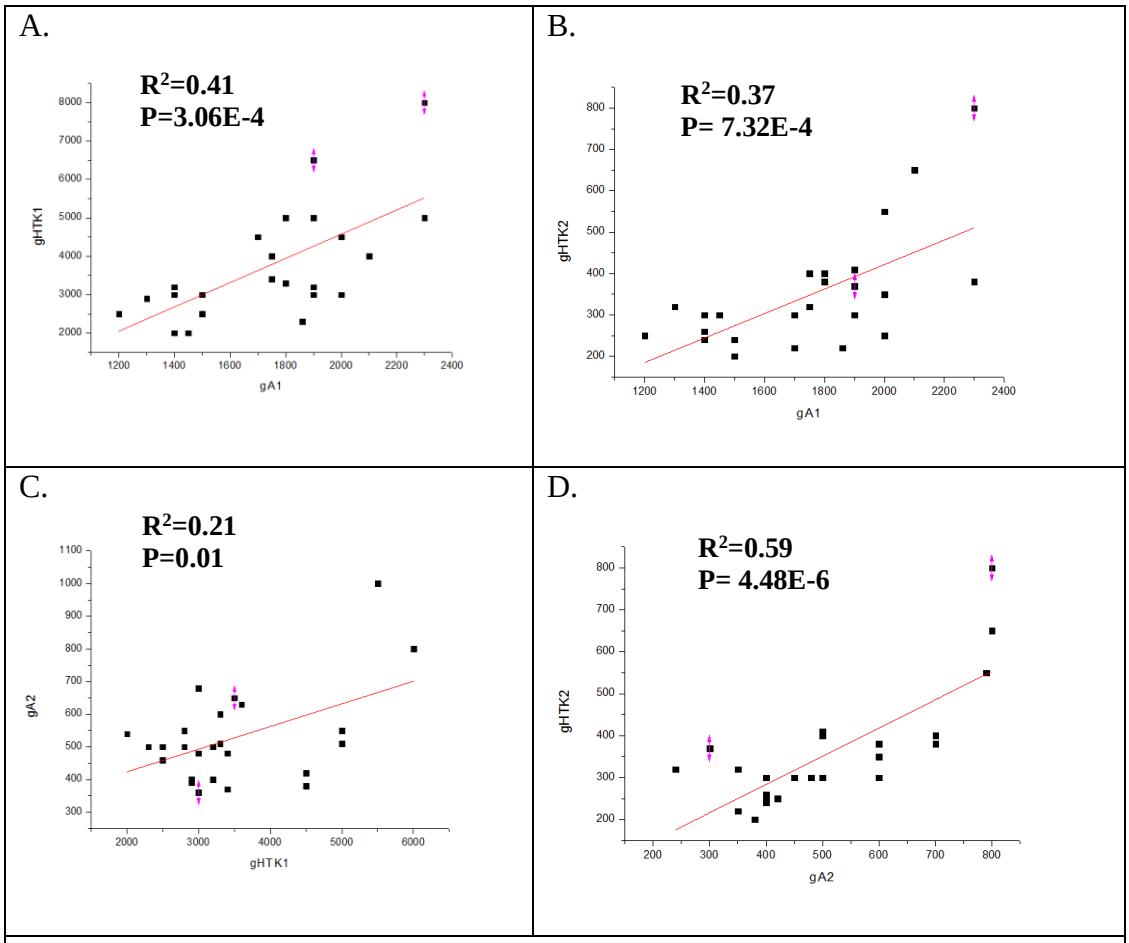


Figure 4. *Correlations between I_A and I_{HTK}.* Shown are the correlation between all four conductance combinations of I_A and I_{HTK}. **A**, shows a statistically significant linear correlation between g_{A1} and g_{HTK1}. **B**, the regression line shows the significant correlation between g_{A1} and g_{HTK2}. **C**, shows the statistically significant correlation between g_{HTK1} and g_{A2}. **D**, the regression line shows a significant correlation between g_{A2} and g_{HTK2}. Ionic conductances are reported in nS.

The relation between the outward current I_A and the inward current I_H

The correlation between I_A and I_H is well established (MacLean et al., 2005, Schulz et al., 2006, Khorkova and Golowasch, 2007, Temporal et al., 2012). In this study, by examining correlations of g_{A1} and g_H, and g_{A2} and g_H from 26 different PD cells, I established positive linear correlations (Figure 5) in both cases. From these results, we

may suggest that both of the two components of I_A have a similar contribution to the correlation between I_A and $I_{H..}$

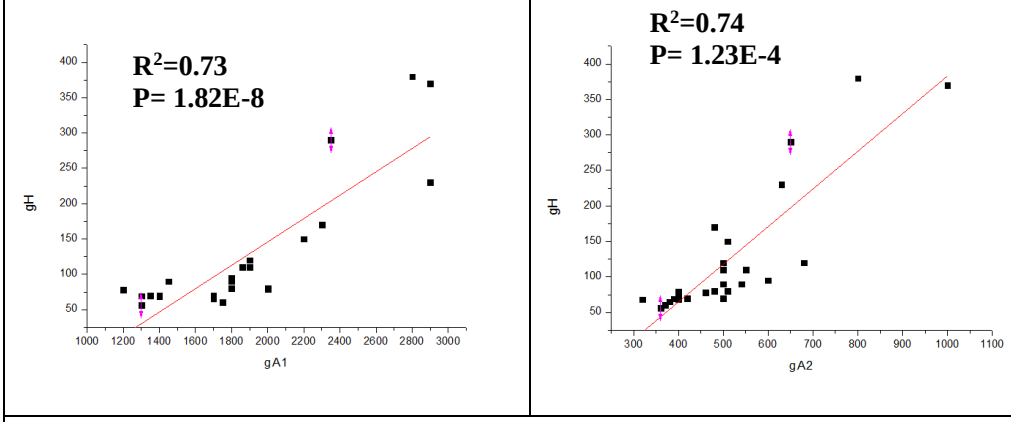


Figure 5. *Correlation between I_A and I_H.* **A**, g_{A1} vs g_H. **B**, g_{A2} vs g_H. Ionic conductances are reported in nS.

The relation between the outward current I_{HTK} and the inward current I_H

Next, I examined correlations between g_H and g_{HTK}. The results show statistically significant correlations between g_{HTK1} and g_H, and g_{HTK2} and $g_{H,,}$ from 24 different PD cells (Figure 6). From Figure 6, the correlation between g_{HTK2} and g_H is stronger than between g_{HTK1} and $g_{H,}$ which suggests an unequal contribution of the two components of I_{HTK} to the relation between I_{HTK} and I_H.

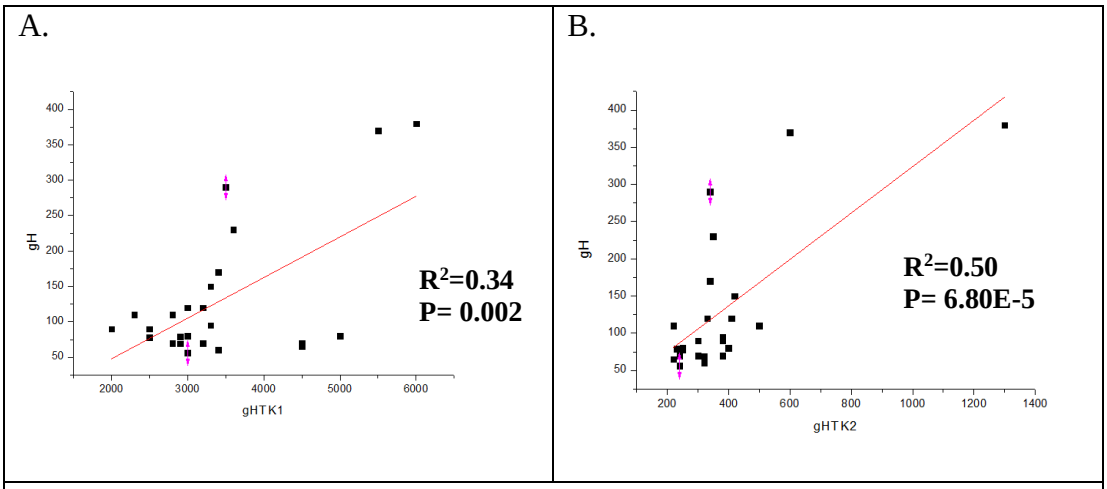
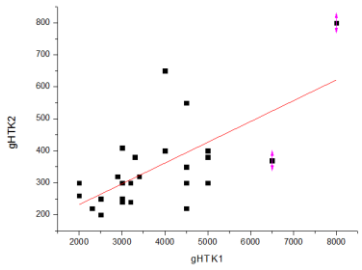


Figure 6. *Correlation between g_{HTK} and g_H.* **A**, shows a significantly positive correlation between g_{HTK1} and g_H. **B**, shows a highly significant correlation between g_{HTK2} and g_H. Ionic conductances are reported in nS

However, the correlation between g_{HTK1} and g_{HTK2} is statistically significant (Figure 7). Based on equation 6, by fitting I_{HTK}, g_{leak}, g_{HTK1}, and g_{HTK2} are determined. I found no significant correlations between g_{leak} and any of the other currents and current components analyzed in this study. Since the correlation between the peak and the steady state of I_{HTK} is significant, I hypothesis that might be a strong correlation between the two components of I_{HTK}: I_{KCa} and I_{Kd} in maximal conductance. To explore in more detail the contributions of the steady state and transient components of I_{HTK}, it was experimentally separated into I_{KCa} and I_{Kd} (See Materials and Methods).



R^2=0.41
P=6.80E-5

Figure 7. *Correlation between peak and steady state of I_{HTK}.* The regression line shows a highly significant correlation. Ionic conductances are reported in nS.

I observed a significantly positively linear correlation between the conductance of I_{KCa} and I_{Kd} (Figure 8) in spite of a low sample number (N=7), which is disproves my original hypothesis that there is no correlation between I_{KCa} and I_{Kd} given the absence of correlation between the mRNA levels that code for these channels. Given our low sample number for I_{KCa} and I_{Kd}, correlations between g_{KCa} and g_{Kd} and the rest of the currents measured are not likely to produce conclusive results. Nevertheless, I examined some of these relationships.

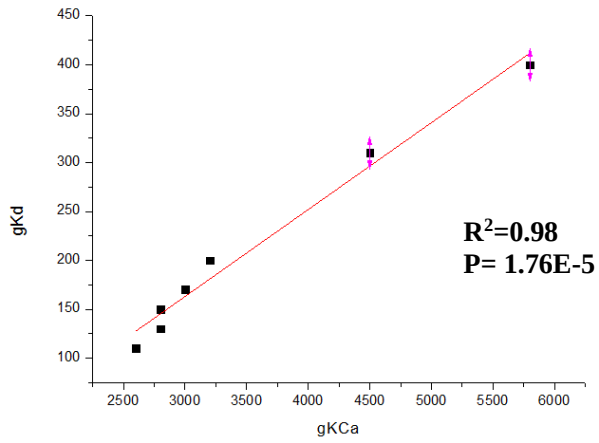


Figure 8. *Correlation between two components of I_{HTK}: g_{KCa} and g_{Kd}.* The regression line here shows a highly significant correlation between them. Ionic conductances are reported in nS.

The relation between I_H and the two components of I_{HTK}: I_{KCa} and I_{Kd}

I_{HTK} and I_H is correlated in amplitude (Khorkova and Golowasch, 2007), in maximal conductance and in mRNA levels (Temporal et al., 2012). But whether the components of I_{HTK} correlated with I_H or which component contributes most to the correlation is not known. In the study, I plotted the maximal conductance of the two currents from 5 different PD cells (See Equations 7, 8), against $g_{H,}$ respectively (Figure 9). The results demonstrated significant linear correlations. g_{Kd} and g_H are much more strongly correlated than g_{KCa1} and g_H, which is consistent with the above results in this study (Figure 6), and the correlation between the conductance of the steady state component of I_{HTK}, g_{HTK2}, and g_H is much more significant than that of the transient I_{HTK} component, g_{HTK1}, and g_H. Since the sample numbers in this portion of the study is so small, even though there is more significant correlation between g_{HTK2} and g_H, we can not simply conclude that I_{Kd} contributes more to the correlation between I_{HTK} and I_H than I_{KCa}. And also we cannot rule out the possibilities that g_A and g_{KCa} has a significant

correlation based on my hypothesis.

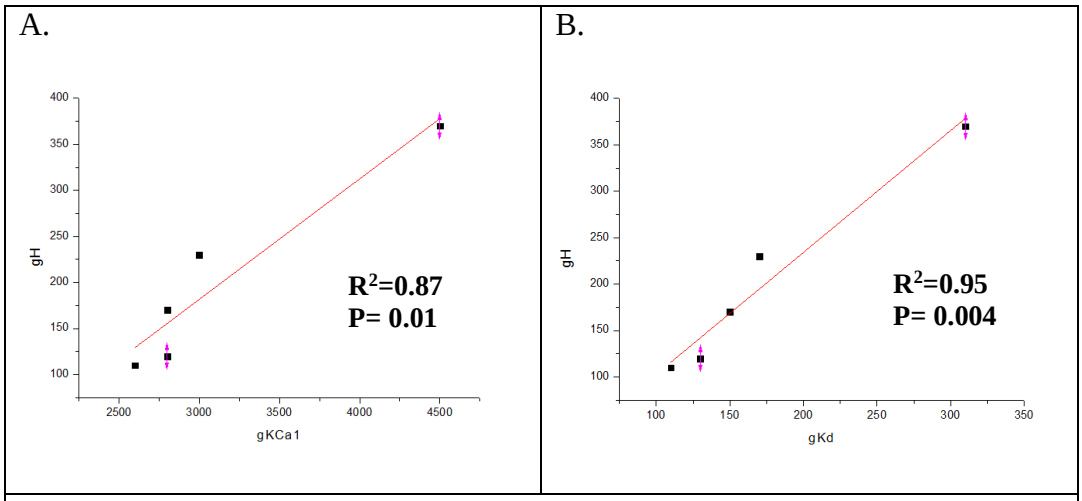


Figure 9. *Correlation between I_H and the two components of I_{HTK} at the maximal level.* **A**, shows a significant correlation between g_{KCa1} and g_H. **B**, shows a highly significant correlation between g_{Kd} and g_H. Ionic conductances are reported in nS.

Discussion:

Correlation between currents at the maximal conductance level

HHfit is a customer developed software that was used to fit ionic currents of crab PD neurons using Hudgkin-Huxley equations. The goal was to test hypothesis that correlations may exist between current parameters, including maximal conductances, activation parameters, and inactivation parameters; and correlations in maximal conductance may exist between I_A and I_{KCa}, I_H and I_{KCa}, while there may be lacking of significant correlations between I_A and I_{Kd}, I_H and I_{Kd}, and I_{KCa} and I_{Kd}.

In this study I could only establish correlations between maximal conductances. There were no significant correlations between any of the other parameters, such as activation or inactivation parameters from these currents (data not shown). This is somewhat unexpected given that at least parameters of activation and inactivation of the same channels would be expected to be correlated.

By using HHfit, the study confirms previously observed correlations between g_A and g_{HTK}, g_A and g_H, g_{HTK} and g_H (Temporal et al., 2012). However, I performed this analysis by also separating the transient and steady state current components of I_A and I_{HTK}. The rationale behind this was as follows:

1) Studies found the two components of I_A: the peak and the steady state may exists intrinsic relations (Connor and Stevens, 1971, Neher, 1971, Cobbett et al., 1989, Cuello et al., 2010), so I hypothesize that there may be correlations between the peak and steady state of I_A.
2) Schulz and colleagues reported that there was no correlation between *BK-KCa* and

shab, *BK-KCa* and *shaw*, *shal* and *shab*, and *shal* and *shaw* in PD neurons (Schulz et al., 2007). Thus, no relationship between the peak and steady state of I_{HTK} was expected.

3) Temporal and colleagues demonstrated a correlation between I_A and I_{HTK}, and a correlation between *shal* and *BK-KCa* (Temporal et al., 2012), since the peak of I_{HTK} is largely generated by I_{KCa}, I hypothesize there may be a correlation between I_A and the peak of I_{HTK}.

Our results show that all four combinations of peak and steady state components of g_A and g_{HTK} are correlated. This is to be expected at least for I_A because there may be an intrinsic protein: the channel itself to regulate the peak and the steady state of I_A, which may ultimately lead to a correlated expression of these two currents. I_{HTK} is known to be composed of two K^+ currents, I_{KCa} and I_{Kd}, and the decomposition into transient and steady state components could be directly linked to these two known ionic currents. In fact, I did uncover a positively linear correlation between g_{KCa} and g_{Kd}. However, this contrasts with the result of Ransdell et al. who reported that I_{Kd} was not correlated with the peak of I_{HTK} (highly representative of I_{KCa}) in crab cardic ganglion (Ransdell et al., 2012). Since it's in a different system, correlations of the same currents may vary distinctly in different systems.

My finding in g_{KCa} and g_{Kd} also contrasts the results at mRNA level reported before (Schulz et al., 2006, Schulz et al., 2007) where no significant correlation between *BK-KCa* and *shab*, and *BK-KCa and shaw* mRNA, which code for I_{KCa} and two forms of I_{Kd} in PD neurons were observed. As I mentioned previously, multiple levels of potential regulations could ultimately lead to correlated expression of ionic currents: at the very least, at the level of transcription, and also at some level between the beginning

of translation, and the full integration of the channel proteins into the plasma membrane. If a coregulation of channel genes ultimately results in a correlated expression of these currents, one possible mechanism is cotranscription. Cotranscription is a simultaneous transcription between two genes and molecular elements which are located closely. If these genes are targeted by the same transcription factors, such as promoters, their expression patterns may tend to be similar, at least at the transcriptional level. Alternatively, translation of these channel's mRNA may be tracking each other, to ultimately lead to the correlated expression of ionic currents. But along the way from transcription, translation and post-translation, there still could occur different modifications of mRNA, protein and ionic channels. This may be a reasonable mechanism to explain the difference between correlations in maximal conductance and in mRNA level (Sutherland and Bickmore, 2009), such as in this case between g_{KCa} and g_{Kd} compared with *BK-KCa* and *shab*, and *BK-KCa* and *shaw*, which are not correlated. A gene may be regulated by many kinds of regulators (Allocco et al., 2004). If the genes I mentioned in this study: *shal*, *BK-KCa*, *shab*, shaw, *H* share multiple regulators, the expression patterns may be more similar. But for some genes, they may have a dominant regulator, which means that the gene expression is only or mostly affected by this regulator. So even if they share multiple regulators, without the same dominant regulators, their expression patterns could be different. What's more, coregulations of genes may not guarantee correlations of ionic current expression because a lot of factors could disrupt or establish coregulations. This would then disrupt (or establish) the ultimately correlated expressions of ionic currents. In the case here for I_{KCa} and I_{Kd}, the difference of correlations between maximal conductance level and mRNA level may be caused by modifications during or after protein translation. One possible mechanism is

co-phosphorylation. The opening of I_{KCa} and I_{Kd} channels may require phosphorylation of the same channel gating protein. This process may serve as a bridge to generate correlated ionic currents. Because this phosphorylation occurs after translation, and *BK-KCa* and *shab* may not co-transcripted or co-translated, thus resulting in the difference of correlations between maximal conductance and mRNA levels.

Other possible mechanisms could be cotranslational interaction of ion channels (Shi et al., 1996), coassembly of ion channels (Frank, 2011, Zhang et al., 2011), cotrafficking by each other into plasma membrane (Vanoye et al., 2010) or direct interactions between ion channels through non-conducting functions (Kaczmarek, 2006).

Since the peak of I_{HTK} is largely generated by I_{KCa}, and I_{HTK} is correlated with I_H, I hypothesized that I_{KCa} is correlated with I_H. The results confirm the hypothesis at maximal conductance level and are consistent with a previous study that reported the coregulation of *BK-KCa* and *H* gene at mRNA level in PD neurons (Schulz et al., 2007). Results also show very significantly positive correlation between g_{Kd} and g_H, which contrasts with mRNA relationships (Schulz et al., 2007). In the Schulz et al. study, *H* was correlated with *shab* in LP and LG neurons, and also correlated with *shaw* in LP neurons. However, they reported no correlation between *H* and *shal* or *shaw* in PD neurons. A mechanism to explain this could be the same as I just discussed above: cotranslational interaction of ion channels (Shi et al., 1996), coassembly of ion channels (Frank, 2011, Zhang et al., 2011), cotrafficking by each other into plasma membrane (Vanoye et al., 2010) or direct interactions between ion channels through non-conducting functions (Kaczmarek, 2006).

Roles of coregulation and correlation in neuronal stability

Neurons have a striking ability to maintain or recover its activity after various forms of disruption (Desai et al., 1999, Cudmore and Turrigiano, 2004, Haedo and Golowasch, 2006). Homeostasis focuses in the capacity of maintain biological system balance under variable conditions and in response to external perturbations. It has been suggested that to maintain homeostasis, variable ionic currents or their conductances may be coregulated, which may be expressed as correlated sets of currents or conductances (Khorkova and Golowasch, 2007, Schulz et al., 2007, Zhao and Golowasch, 2012). Therefore, how the correlated ionic currents and coregulated channel genes carry out their roles to maintain homeostasis is vitally important. However, so far, the underlying mechanisms is poorly understood.

Studies have reported coregulations of ionic current genes (MacLean et al., 2003, MacLean et al., 2005, Schulz et al., 2006, Schulz et al., 2007), correlations of ionic current (Khorkova and Golowasch, 2007, Temporal et al., 2012), but there are no clearly defined mechanisms to explain the exact roles of coregulation and correlation in neuronal stability.

MacLean and colleagues demonstrated that the role of coregulation in lobster STG could be compensatory homeostasis (MacLean et al., 2005). They found that neuronal activity was maintained constantly even with a dramatic increase of I_A. The role of coregulation in crab STG probably the same as it is in lobster STG (MacLean et al., 2005). Coregulation of *shal* and *H*, and *BK-KCa* and *H* may play a role in compensatory homeostasis because they correspond to oppositely flowing currents. However, other roles of coregulation may exist in crab STG. For instance, *shal* and *BK-KCa* (and the corresponding I_A and I_{HTK}) are positively correlated in PD neurons, but both of them

correspond to outward currents, i.e. an increase of I_A will concomitantly increase I_{KCa}. So how could this coregulation stabilize neuronal activity? One possible mechanism might be that the positive coregulation of *shal* and *BK-KCa* is positively coregulated by other mechanisms, such as activity-dependent channel gene expression, which corresponds to an inward current. As a consequence, the increase of the positive coregulations of two outward could compensate for the increase of the other inward current to maintain stable neuronal activity.

Correlation may also play an important role in neuronal activity. A recent study reported that ionic current correlations may influence neuronal activity attributes (Zhao and Golowasch, 2012), which may explain why correlations of currents are cell type specific, at least in maximal conductance.

Coregulation and correlation may be associated with intracellular signaling pathway. Amendola and colleagues found that intracellular Ca^{2+} and cytosolic cAMP act to alter the cell-type specific variations between I_A and I_H and also shift I_A and I_H coordinatedly in SNc dopaminergic neurons (Amendola et al., 2012). Kv4.3 channels, which are members of voltage-gated A-type potassium channels (termed Shal channels), and also a *shal* gene related subfamily (An et al., 2000), are related with calcium sensitive auxiliary subunit KChip3.1 in the SNc dopaminergic neurons (Liss et al., 2001). Kv4.3 and KChip3.1 together can mediate the fast-inactivation of the A-type potassium channel in dopaminergic neurons. So intracellular Ca^{2+} level may modulate the properties of I_A, decrease the inward current I_A, which has also been reported in other systems (Patel et al., 2002, Anderson et al., 2010). HCN1, HCN2 and HCN4 are three subunits of non-selective cation HCN channels (Monteggia et al., 2000) responsible for I_H in SNc dopaminergic neurons. Among the three subunits, HCN2 and HCN4 are

modulated by intracellular cAMP. What's more, the relation between calcium and cAMP is found because two adenylyl cyclases, which are the enzymes that catalyze the conversion from ATP to cAMP, can be inhibited by calcium in SNc dopaminergic neurons. So in SNc dopaminergic neurons, the increase of intracellular Ca^{2+}, which could decrease I_A, will inhibit the formation of cAMP, thus decrease cAMP relative I_H. Based on the above background, the research group reported that the correlation of I_A and I_H in SNc dopaminergic neurons, are Ca^{2+}/cAMP-sensitive (Amendola et al., 2012). Ca^{2+} is known to activate I_{KCa} (Gola and Crest, 1993, Robitaille et al., 1993, Marrion and Tavalin, 1998, Vergara et al., 1998) while I_A would decreased during the increasing of intracellular Ca^{2+} (Coetzee et al., 1999). As stated before, the increase of Ca^{2+} would inhibit cAMP formation, therefore, with the reduction of I_A, I_H is reduced, while I_{KCa} is upregulated. Modification of protein kinase-related and or cyclic nucleotide-related mechanisms will modify I_A and I_{KCa} channels (Alkon et al., 1982, Poulain et al., 1994, Enyeart et al., 1996, Yao and Wu, 2001). Peng and Wu (2007) also reported a homeostatic regulation of K^+ currents via the coregulation of Shaker-type I_A and I_{KCa} in *cac* neurons in *Drosophila* mediated by Ca^{2+} (Peng and Wu, 2007).

A recent study found in both STG and cardiac ganglion, the genes that encode I_A and I_{KCa} are positively correlated, but the currents in cardiac ganglion neurons are negatively correlated (Ransdell et al., 2012). Clearly, the post-translational regulation mechanism must be different. In STG I_A is not known to be calcium-dependent, nor affected by calcineurin activity, which may suggest a distinct mediation of coregulation in these different systems within the same animal. The finding in Ransdell et al. study is similar to what was observed in fly neurons with the reduction of I_{KCa}, I_A is upregulated (Peng and Wu, 2007), but opposite to what was observed in crab STG

neurons (Temporal et al., 2012). Due to the negative correlation, the increase of I_{KCa} will lead to the decrease of I_A, which may act as compensatory role to stabilize cellular excitability and network output. However, this contrasts with my finding and previous findings in STG system: I_A is positively correlated with I_{HTK}, with the increase of I_A, I_{HTK} is upregulated. Different systems may have different mechanisms to maintain homeostasis, so how could this lead to homeostasis in STG system? One possible explanation is that the positive correlation between I_A and I_{HTK} in maximal conductance might be correlated negatively with activity-dependent conductance changes, and the changes would ultimately compensate for the sum of the changes of g_A and g_{HTK}. This may also offer a reasonable explanation that g_{KCa} and g_{Kd} is positively correlated while the neuronal activity maintain stable.

Conclusions and Further Studies

By using HHfit, I confirm the results shown previous studies: the correlation between I_A, I_{HTK}, I_H in maximal conductance (Schulz et al., 2006, Khorkova and Golowasch, 2007, Schulz et al., 2007, Temporal et al., 2012). Even though there are no significant correlations between other parameters such as activation parameters, inactivation parameters, HHfit is indeed another way to establish correlations between currents, at least in maximal conductance. My hypothesis that g_{KCa} and g_H may be correlated based on the study by Schulz et al (Schulz et al., 2007) was confirmed by using this method. However, I did report new findings which were different from my hypothesis based on previous studies. I found the correlation between I_{KCa} and I_{Kd}, which is different from the mRNA examination in PD neurons (Schulz et al., 2007). The results here

demonstrated a significant correlation between g_{Kd} and g_H which contrasts with the results in mRNA level in PD neurons (Schulz et al., 2007).

In further studies, we can use HHfit to analysis more currents with sufficient samples in different neuron types such as LP, IC and other neurons of the pyloric network. This may allow us to establish correlations between other current parameters aside from maximal conductance, because currents correlations and variability may vary dramatically in different types of neurons.

Appendices:

Tables:

Table1. Maximal Conductance of IA and IHTK in PD neurons

Cell Number	g_{A1}	g_{A2}	g_{HTK1}	g_{HTK2}
#090930	2300	800	8000	800
#91005	2300	700	5000	380
#91008	1750	700	4000	400
#91012	1400	400	2000	260
#91020	2100	800	4000	650
#91023	1500	400	3000	240
#91029	1800	500	5000	400
#91102	1900	500	5000	300
#91103	1700	350	4500	220
#91104	1700	450	4500	300
#91110	2000	600	4500	350
#91202	1500	380	2500	200
#91207	1800	600	3300	380
#91210	2000	790	4500	550
#91211	1200	420	2500	250
#100413	2000	400	3000	250
#100420	1450	480	2000	300
#100517	1400	400	3000	300
#100527	1900	500	3000	410
#100609	1900	600	3200	300
#100622	1750	350	3400	320
#100623	1860	350	2300	220
#100628	1300	240	2900	320
#100820	1400	400	3200	240
#100909	1900	300	6500	370

Table2. Maximal Conductance of IA and IH in PD neurons

Cell Number	g_{A1}	g_{A2}	g_{H}
#91023	1300	360	56
#91029	1800	510	80

#91103	1700	380	65
#91104	1700	420	70
#91207	1800	600	95
#91211	1200	460	78
#100413	2000	480	80
#100420	1450	540	90
#100527	1900	680	120
#100622	1750	370	60
#100623	1860	500	110
#100628	1300	390	69
#100820	1350	400	70
#120106	1800	500	90
#120410	1400	500	70
#120521	1700	400	68
#120607	1400	320	68
#120924	2800	800	380
#120925	1900	500	120
#121002	1900	550	110
#121003	2300	480	170
#121009	2200	510	150
#121010	2900	630	230
#121015	2000	400	79
#121016	2900	1000	370
#121017	2350	650	290

Table3. Maximal Conductance of IHTK and IH in PD neurons

Cell Number	g_{HTK1}	g_{HTK2}	g_H
#91023	3000	240	56
#91029	5000	400	80
#91103	4500	220	65
#91104	4500	300	70
#91207	3300	380	95
#91211	2500	250	78
#100413	3000	250	80
#100420	2000	300	90
#100527	3000	410	120
#100622	3400	320	60
#100623	2300	220	110
#100628	2900	320	69
#100820	3200	240	70
#120106	2500	380	90
#120410	2800	380	70

#120924	6000	1300	380
#120925	3200	330	120
#121002	2800	500	110
#121003	3400	340	170
#121009	3300	420	150
#121010	3600	350	230
#121015	2900	230	79
#121016	5500	600	370
#121017	3500	340	290

Table4. Maximal Conductance of Ikca and Id in PD neurons

Cell Number	g_{KCa}	g_{Kd}
120924	5800	400
120925	2800	130
121002	2600	110
121003	2800	150
121008	3200	200
121010	3000	170
121016	4500	310

Table5. Maximal Conductance of Ikca, Id and IH in PD neurons

Cell Number	g_{KCa}	g_{Kd}	g_{H}
#120925	2800	130	120
#121002	2600	110	110
#121003	2800	150	170
#121010	3000	170	230
#121016	4500	310	370

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