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Literature Review

Ion channel correlations in neurons: An integrative review

INTRODUCTION

Correlations between membrane ion channels, on the level of conductance densities and gene expression, are found across phyla (Tran et al., 2019). These correlations are useful in maintaining consistent activity in neurons in the face of high variability in neural membrane ion channel expression and density, and constantly changing internal and external conditions (Bergquist et al., 2010, MacLean et al., 2003, O'Leary et al., 2013). The existence of correlations may represent a mechanism by which homeostatic regulatory features may enforce and stabilize desired activity in specific neurons (Ball et al., 2010, Burdakov 2005, MacLean et al., 2005, Schulz et al, 2007). Homeostatic mechanisms are able to reliably influence coregulation of ion channel pairs over different time-scales by changing the properties of correlations, including slope, strength, and set-points within the parameter space (Stein 2009, Soofi et al., 2012, Temporal et al., 2012, Tran et al., 2019). Two key mechanisms for regulation of firing rate activity include neuromodulation and activity-dependent feedback, both of which influence the maintenance of many properties of neural activity, as well as the conservation and maintenance of ion channel correlations. (Temporal et al., 2014). Neuromodulation is defined as modulation of intrinsic firing rate properties of circuit neurons and alteration of synaptic strength by neuromodulatory substances, such as local hormones, and activity-dependent feedback is defined

as the response of a neuron to its own internal state (Marder 2012). In this review, the relationship of variability in mRNA levels and conductance densities**,** neuromodulation of neuronal properties , and activity-dependent homeostasis to the distinct correlations between ion channels will be explored in order to inform future work and identify presently unanswered questions.

VARIABILITY OF MRNA LEVELS AND CONDUCTANCE DENSITIES ACROSS CELL TYPES AND SPECIES

Individual ion channel mRNA transcripts and maximal conductance values can vary several-fold, even in neurons of the same type (Liu et al., 1998, Golowasch et al., 1999, Schulz et al., 2006, Swensen and Bean 2005). This phenomenon occurs across many different species and types of neurons, ranging from neurons in the stomatogastric ganglion (STG) to Purkinje cells in the cerebellum and dopaminergic cells in the substantia nigra (Schulz et al., 2006, Swensen and Bean 2005, Liss et al., 2001). This level of variation is found in both the mRNA transcripts correlated to the ion channel proteins, as well as the maximal conductance values of ion channels (Schulz et al., 2006, Baro et al., 1997). In I_H-type currents, voltage for half-activation showed an almost 20mV difference between cell types in the pyloric network of the lobster STG (Peck et al., 2006). K^+ currents in the inferior cardiac neurons in *Cancer borealis* displayed two- to five-fold variation in current densities (Golowasch et al., 1999). In dopaminergic neurons in the substantia nigra, there was found an eightfold variation in I_A current density and five- to ten-fold variation in mRNA expression (Liss et al., 2001). The difference in variability between current density and mRNA expression highlights the complexity of current generation, wherein the

biophysical properties of the neuron are regulated by gene expression patterns, post-transcriptional events, and post-translational events (Hille 2001).

The variability in mRNA levels and maximal conductance in neurons, even of the same type, highlights a pressing issue present research is grappling with: why do these forms of variability manifest when neurons of the same type are tuned toward specific patterns of activity? Though this has yet to be confirmed, there are a number of hypotheses that cover different aspects of the problem. Variability in channel expression and current density may reflect the tuning of conductances required to maintain target activity over a long period of time (Marder and Goaillard 2006, Schulz et al., 2006). This may arise during all periods of the life of a neuron, or it may be specific to initial development. In the STG, it has been theorized that tuning rules governing development of neurons may result in networks that are highly variable across individuals by the time neural networks are fully developed (Marder and Rehm 2005, Rehm et al., 2008, Rehm et al., 2008). It may be the case the variability is an innate noise resulting from high numbers of small-molecule interactions that build over the lifetime of the neuron (Ozbudak et al., 2002, Raser and O'Shea 2005). Along with this, variability in other systems may induce variability in ion channel expression and current densities as well -- the variability of transcriptional machinery and regulatory transcriptional sequences, then, can lead to variability in gene transcription, and subsequently ion channel expression (Blake et al., 2003, Volfson et al., 2006).

HOMEOSTASIS OF NEURONAL ACTIVITY

Despite high variability within neurons of the same type, as well as influx of a variety of endogenous and environmental perturbations, neurons are able to maintain reliable patterns of activity (Desai et al., 1999, Golowasch et al., 1999, LeMasson et al., 1993, Turrigiano et al., 1994, Turrigiano et al., 1995, Turrigiano 1999, Turrigiano et al., 1998). Neurons, acting synergistically with their neuromodulatory environments, have the ability to utilize compensatory mechanisms to stabilize activity on a long time-scale (Ma'ayan et al., 2005, Ma'ayan et al., 2005). Compensatory mechanisms including neuromodulation and activity-dependent feedback improve robustness in neurons and neural networks by widening the range of characteristic sets of mRNA levels and conductance densities that produce desired activity and increasing the extent to which a neuron or network can be perturbed without resulting in permanent loss of desired activity (Rodgers et al., 2013, Goldman et al., 2001). Neuronal plasticity is regulated by a target level of excitability (Liu et al., 1998, LeMasson et al., 1993, Turrigiano and Nelson 2004). Cells manifest plasticity in neuronal excitability through the use of two or more mechanisms -- neuromodulation and activity-dependent feedback (Cudmore and Turrigiano 2004, Desai et al., 1999, Li et al., 2004, Loebricha and Nedivi 2009, Zhang and Linden 2003). Both mechanisms are necessary for regulation of firing rate activity (Temporal et al., 2014). These compensatory mechanisms can change ionic channel properties, such as maximal conductance densities, mRNA transcript levels, and downstream, firing rate activity (Zhang and LInden 2003, Misonou et al., 2006, Daoudal and Debanne, 2003), change spatial distribution/localization of ion channels (Shah et el., 2010, Misonou et al., 2004), and associate channels with subunits which can modify them (Marionneau et al., 2012, Kim et al., 2008).

It has shown that control of rhythmic activity in the STG is dependent on neuromodulators which are released from adjacent ganglia (Luther et al., 2003, Thoby-Brisson and Simmers 2002). Along with that, neuromodulators can have paracrine actions on pyloric neurons in the STG, resulting in regulation of activity over both short- and long-time scales (Swensen and Marder 2001). This regulation is brought about by second messenger-mediated signaling pathways, which alter ionic maximal conductances (Nadim and Bucher 2014, Marder 2012) and the expression of microRNAs (Krenz et al., 2014, Krenz et al., 2015). For example, neurons can increase I_A current density in response to dopamine binding to low-affinity D1 receptors (Krenz et al., 2013). Loss of neuromodulatory input can result in loss of functional output, as well as desynchronized activity (Ransdell et al., 2013).

In order for neurons to maintain stable and desirable output, control of ion channel turnover must be regulated by a mechanism which is reliant on the firing properties of the neuron (LeMasson et al., 1993, Liu et al., 1998, Stemmler and Koch 1999). Activity-dependent feedback results in compensatory plasticity changes to neuronal excitability resulting from what are often prolonged changes in firing activity, making it an ideal candidate for self-regulation of neuronal properties (Daoudal et al., 2003). Activity-dependent feedback can result in changes to both channel mRNA levels and conductance densities themselves (Temporal et al., 2014, Haedo and Golowasch 2006, Turrigiano et al., 1994, Turrigiano et al., 1995).

Evidence of activity-dependent feedback has been found across multiple experiments. Notably, Temporal et al. discovered that decentralization of the STG followed by application of pilocarpine resulted in maintenance of activity that was lost with decentralization alone (2014). The network could suffer the loss of a large number of modulatory inputs and still maintain its

activity in the presence of a single exogenous substance, indicating that activity-dependent feedback likely influenced the regulation of activity of the network (Marder 2012). Along with that, lobster STG neurons which were chronically isolated from modulatory input recover endogenous bursting due to changes in intrinsic membrane conductances, indicating the presence of an activity-dependent mechanism (Turrigiano et al., 1994, Turrigiano et al., 1995). Individual neurons can regulate ionic currents in activity-dependent manners as well. High-affinity D1 receptors respond to dopamine in very low concentrations and regulate I_H in an activity-dependent fashion (Krenz et al., 2013, Krenz et al., 2015, Rodgers et al., 2011).

In computational models, activity-dependent tuning rules have been shown to reliably result in desired activity (O'Leary et al., 2013, LeMasson et al., 1993, Liu et al., 1998). These conductance-based models generate outputs via changes in conductance expression as a result of cell-type specific channel expression rates (O'Leary et al., 2014).

ION CHANNEL CORRELATIONS

Though ion channel correlations are not theoretically required to maintain neural activity, they are nonetheless present ubiquitously across phyla, theoretically reduce necessary complexity of homeostatic mechanisms, and experimentally have been shown to be significantly affected by homeostasis (Taylor et al., 2009, Tran et al., 2019, Baumgardt et al., 2007, Stein 2009, Soofi et al., 2012, Temporal et al., 2012). Coregulated ion channels are effective in generating consistent activity despite high variability across cell types (Bergquist et al., 2010, MacLean et al., 2003, O'Leary et al., 2013). In and of themselves, ion channel correlations can enforce ion channel ratios to properly maintain specific activity features (Schulz et al., 2007,

MacLean et al., 2005, Ball et al., 2010, Burdakov 2005). Along with that, ion channel correlations are a potent candidate for characterization of neuronal identity, given that cellular output is determined by characteristic sets of correlated ion channel gene expressions and conductance densities (Schulz et al., 2007, O'Leary et al., 2013, O'Leary et al., 2014). Correlations between ionic current amplitudes allow neurons of any type to manifest strikingly similar patterns of activity despite widely variable relative abundances of current types (Olypher and Calabrese 2007, Rotstein et al., 2017, Hudson and Prinz 2010, O'Leary and Marder 2016, Lamb and Calabrese 2013).

Examples of ion channel correlations are well documented within cell types and across species. I_H and I_A-current types consistently occur in a set ratio in their amplitudes (MacLean et al., 2003, MacLean et al., 2005). Removal of I_{Ca} causes compensatory decrease in I_{KCa} and I_A that is independent of kinetic channel properties (Peng and Wu 2007). In the pyloric dilator (PD) neurons in the STG, channel conductances are highly correlated, as well as mRNA levels, and there is even considerable overlap between the two (Temporal et al., 2011). This exemplifies that there is not only a link between specific channel conductances or mRNA levels, but a functional link between regulation of mRNA levels and channel membrane conductance levels.

Neuromodulation has been shown to be essential for the maintenance of correlations between ion channels (Temporal et al., 2014). However, it is contentious whether or not activity-dependent feedback mechanisms influence these correlations. A large body of research indicates that activity does influence the expression of ion channels (Cudmore and Turrigiano 2004, Turrigiano et al., 1994, Desai et al., 1999, Golowasch et al., 1999, Haedo and Golowasch 2006, Li et al., 2004, Loebrich and Nadivi 2009, Zhang and Linden 2003).

CORRELATIONS IN MRNA TRANSCRIPT LEVELS

It is clear that ion channels are correlated at the level of mRNA expression (Schulz et al., 2007). They have been shown in the cardiac ganglion in the crustacean, as well as the stomatogastric ganglion (Tobin et al., 2009, Baro et al., 1997, Schulz et al., 2006, Schulz et al., 2007, Temporal et al., 2011). Along with that, correlations have been shown to not be more similar within an animal than across a population, indicating genetic conservation of ion channel correlations (Tobin et al., 2009). Different cell types generally express different quantitative relationships of expression of ion channels, indicating that sets of correlated ion channels can determine functional output of a neuron (Schulz et al., 2006, Schulz et al., 2007, Temporal et al., 2014). There is accompanying evidence that the neuromodulatory environment of a neuron determines correlations of mRNA levels (Temporal et al., 2011).

There is significant support that neuromodulation influences correlations of mRNA levels (Temporal et al., 2011, MacLean et al., 2003, MacLean et al., 2005). MacLean et al. showed that overexpression of *Shal* in the STG resulted in a significant increase in I_A that did not result in significant effect on functional output due to a compensatory change in I_H that was independent of activity (2013, 2015). This provides further evidence to the theory that there is direct co-regulation between *Shal* and I_H that results in stabilization of functional output (MacLean et al., 2005, Hudson an Prinz 2010). Along with this, loss of neuromodulatory input due to decentralization has been shown to destroy, alter, or augment the strength and slope of correlated mRNA levels (Temporal et al., 2011).

CORRELATIONS IN CONDUCTANCE DENSITIES

Ion channel correlations can also exist independently of mRNA transcript levels, at the level of conductance densities (MacLean et al. 2003, Tran et al., 2019). The PD neurons and the lateral pyloric (LP) neurons have been shown to possess correlated levels of I_H, I_A, and I_{BKKCa}, and are altered in a cell-specific manner by perturbation (Temporal et al., 2012). This data provides further evidence that H- and A- type currents are coregulated, both at the level of mRNA transcripts and conductance densities. Along with mRNA levels, similar patterns of activity have been shown to be produced by quantitative combinations of maximal conductances for different ion channels (Goldman et al., 2001, Golowasch et al., 2002, Prinz et al., 2004, Schulz et al., 2006, Swensen and Bean 2005, Tobin et al., 2006, Achard and DeSchutter 2006).

Neuromodulation can influence coexpression of ion channels at the level of maximal conductances (Tobin et al., 2009). It is, however, contentious whether or not activity-dependent feedback mechanisms can influence these correlations. In models, activity-dependent mechanisms have been shown to generate and regulate biophysically realistic dynamics of neurons in the STG (O'Leary et al., 2013, O'Leary et al., 2014, Liu et al., 1998, LeMasson et al., 1993). Along with that, experimental data has shown that inhibition of I_A results in compensatory increase in I_{BKKCa} that is dependent on intracellular calcium concentration and calcineurin activity, but is independent of calcium in the presence of TEA (Ransdell et al., 2012). The potential dependence of this compensatory mechanism on calcium provides evidence that activity-dependent feedback can influence ion channel correlations (Turrigiano et al., 1994, Turrigiano et al., 1995). In opposition to this data, Temporal et al. argued that coexpression of ion channels is not influenced by intrinsic properties of the neuron, on the basis that

neuromodulatory input can successfully destroy correlations between ion channel mRNAs (2011).

MECHANISMS OF CORRELATIONS

It is clear that neuromodulation can influence coregulation of pairs of ion currents and mRNA levels, and that neuronal activity can be determined by sets of correlated expressions of ion channel genes (Stein 2009, Soofi et al., 2012, Temporal et al., 2012, Schulz et al., 2007). Though there are many aforementioned benefits to coregulation of ion channels, it is currently unknown what mechanism drives their existence in biological systems. Membrane voltage activity has been shown to be a parameter by which ion channel relationships can be coordinated and maintained (Santin and Schulz 2019). It has been argued by Sutherland and Bickmore that cotranscription and close proximity of transcriptional elements may be a large factor, given that proximity increases the likelihood of simultaneous transcription (2009). Along with that, cotranslational interaction, co-trafficking of ion channels into the membrane, and coassembly of ion channels to become larger complexes may also be suitable candidates for the mechanisms that drive the existence of correlations between ion channels (Shi et al., 1996, Vanoye et al., 2010, Arcangeli 2011, Frank 2011, Zhang and Golowasch 2011). It is possible, as well, that interactions of ion channels via nonconducting properties may be a suitable mechanism (Kaczmarek 2006).

Theoretical work has suggested that correlations are simply an emergent property of homeostatic tuning rules (O'Leary et al., 2013). Other work has indicated that correlations may simply be present for developmental regulation, on the basis that they are not necessary for

maintenance of neural activity (Taylor et al., 2009). In opposition, MacLean et al. suggested that modulating I_A current densities or I_H current densities alone would change the functional output of the neuron, and that modulating both was necessary for maintenance of desirable activity (2005).

Ion channel correlations have proven a significant challenge to models of neurons with homeostatic regulation. Sets of correlations are dissimilar across cell types, making generalizability a big challenge, and without an understanding of the functional mechanism driving their existence, or the biological mechanisms underlying both neuromodulation and activity-dependent feedback, creating biophysically realistic models is exceptionally difficult (Schulz et al., 2007).

Previous models have focused primarily on activity-dependent mechanisms, rather than a combination of simulated neuromodulatory environments in combination with activity-dependent feedback (O'Leary et al., 2013, O'Leary et al., 2014, Liu et al., 1998, LeMasson et al., 1993). These models have consistently relied on calcium as a sensor for activity-dependent feedback. Some experiments suggest that calcium is a sensor by which neurons can utilize activity-dependent feedback (Turrigiano et al., 1994, Turrigiano et al., 1995). On the other hand, it has been shown that blocking I_{BKKCa} and I_{Kd} with TEA resulted in calcium-independent compensatory increase in I_A currents in the cardiac ganglion of *Cancer borealis,* suggesting that calcium is, at minimum, not the only sensor required for activity-dependent feedback (Ransdell et al., 2012) Regardless, it is apparent that both neuromodulation and activity-dependent feedback are required for maintenance of emergent correlations between ion channels (Temporal et al., 2014).

The real correlations between ion channels have not been successfully reproduced, or theoretically simulated in a realistic context (Schulz et al., 2006, Schulz et al., 2007, O'Leary et al., 2013, O'Leary et al., 2014, Liu et al. 1998). O'Leary et al. reproduced correlations between ion channels, but failed to show the diversity of these correlations, in that not all ion channels are correlated in reality (2014). The variety of correlations found in reality have not been reproduced with the use of only a single sensor, but can be with the use of multiple sensors (O'Leary et al., 2014, Liu et al., 1998).

CONCLUSIONS

Neurons display significant variability in ion channel conductances and mRNA transcript levels across cell types and species, must maintain reliable functional output in the face of varying endogenous and environmental circumstances, and synchronize to other neurons to form networks which have collective output. These ion channel correlations have been suggested to reduce the complexity of homeostatic mechanisms, and have been shown to have explicit roles in mediating the relationships of opposing ionic currents, particularly in I_A- and I_H-type currents (Baumgardt et al., 2007, MacLean et al., 2003, MacLean et al., 2005). Many questions still remain, however.

How do activity-dependent feedback and neuromodulation influence ion channel correlations? What is the mechanism driving the existence of coregulation? What are the mechanisms underlying activity-dependent feedback that allow for the manifestation of correlations with varied slopes, multiple functional characteristic sets, and cotransmitter-mediated existences? Computational models can discover the potential principles

of correlations that result in manifestation of robust, stable neurons and neural networks. A synergy of existing experimental sets with plausible models able to successfully reproduce them may grant insight into the total minimum number of activity-dependent feedback sensors, or the neuromodulatory environments required for the maintenance of coregulation of ion channels.

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