DIFFERENCE BETWEEN PROTOTYPICAL AND ARKYPALLIDAL GLOBUS PALLIDUS NEURON AND THE EFFECT OF ALCOHOL

by

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Prototypical……...Proto
Arkypallidal ..... Arky
Globus Pallidus ..... GP
Picoampere……..…….pA
Nanoampere……..……nA
Persistent Sodium channel .....Nap
Hyperpolarizing-activated cyclic nucleotide ..... HCN
Small conductance calcium activated potassium channel ..... SK channel
Low voltage activated Potassium permeable channel…….……Kv4
Calcium and voltage activated potassium channel…….….BKCa

ABSTRACT

DIFFERENCE BETWEEN PROTOTYPICAL AND ARKYPALLIDAL GLOBUS PALLIDUS NEURON AND THE EFFECT OF ALCOHOL

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George Mason University, 2017

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Alcoholism and alcohol abuse is a severe problem. An increase in the blood ethanol concentration affects the function of many parts of the brain, including the Basal Ganglia, which is critical for goal directed and habitual behavior. The Globus Pallidus (GP) is a part of the Basal Ganglia and funnels the output from the striatum, the input part of the Basal Ganglia. The GP is further divided into the internal Globus Pallidus (GPi) and external Globus Pallidus (GPe). There is compelling evidence suggesting that the pathological activity of GPe contributes to the motor symptoms of a variety of movement disorders like Parkinson's disease, and that GPe activity is affected by ethanol. Recently it was discovered that the GPe is comprised of multiple cell types, with an activity based subdivision into prototypical neurons and arkypallidal neurons. This distinction is important because the firing rate of arkypallidal neurons is lower than that of prototypical neurons. Furthermore, arkypallidal neurons innervates the striatum, resulting in negative

feedback, whereas the prototypical neuron innervates the sub thalamic nucleus which is an output pathway. Ethanol affects the open probability of the calcium dependent potassium channel (BKCa) and reduces the firing rate of the arkypallidal, but not prototypical neurons. We computationally modeled these neurons in the neural modeling software MOOSE to determine the factors causing the difference in the firing rate. My results show that the three channels demonstrated to differ between the two neuron types (Hernandez et.al 2015) are not enough to explain the difference in the firing rate of the two neurons but there are other channels which are responsible for the lower firing rate of the arkypallidal neuron. To simulate the effect of ethanol, we increased the BKCa current and the results showed that the firing rate decreased when the BKCa current increased only in the arkypallidal neurons that have a substantially higher BKCa density. In summary, based on our simulations, we argue that there are other factors that affect the firing rate of the GP neuron and provides a foundation for further studies to determine the difference between the prototypical and arkypallidal GP neuron and the effect ethanol has on the neurons.

INTRODUCTION

Alcoholism and alcohol abuse are a big social problem with severe health consequences. Chronic alcohol consumption leads to high blood ethanol concentration which then alters the function of several brain regions including the basal ganglia. One behavioral aspect of alcohol is a decrease in executive control of behavior and an increase in habitual use. In addition, the tendency to relapse after withdrawal impairs long term success of withdrawal treatments. Even more disturbing is the observation that abstinence though being crucial for recovery contribute to more compulsive drinking after relapse (Becker and Lopez, 2004s; Lopez and Becker, 2005).

The basal ganglia is a set of subcortical nuclei involved in both goal directed action control and habitual behavior (Lindahl et al., 2016; Albin et al.,1995; Graybiel,2008; Redgrave et al.,2010; Turner & Desmurget,2010; Costa.2011; Gerfen & Surmier,2011; Kravitz et al. 2012). The major input station of the basal ganglia is the striatum which influences a variety of functions such as action learning, performance, emotion and the development of habitual performance. The striatum projects to the globus pallidus (GP) and substantia nigra (SNR), and through these projections, the striatum influences the thalamus and cortex. The GP is in a unique position and acts as a gateway for striatal output. An increase in blood ethanol concentration influences the function of striatum (Chen et al., 2011). Specifically, acute alcohol enhances GABA

release in the striatum (Dopico and Lovinger, 2009; Kumar et.al., 2009). There are many GABA receptors in the GP and thus alcohol may have an effect here also. June et.al. (2003) showed that acute alcohol affects the GABA receptors in the GP and Nikolaou et al. (2013) showed that ethanol decreases activity of GP neurons.

The GP is subdivided into internal and external (GPi and GPe) segments. Until recent times it was thought that the GPe has a uniform cellular composition and acts as a relay in the basal ganglia (Albin et al., 1989; Alexander & Crutcher ,1990; DeLong,1990; Albin et al.,1995; Joel & Weiner,1997). But newer findings have shown that the GPe is comprised of several types of neurons. They are classified based on electrophysiological properties into prototypical (proto) and arkypallidal (arky) neurons. The arkypallidal neuron project to the striatum while prototypical neurons project to the subthalamic nucleus (STN) (Mallet et al.,2012). Arkypallidal neurons have also been shown to have a lower firing rate (Abdi et.,2015; Dodson et al.,2015).

Another method of classification of GPe neurons is via biochemical markers. Multiple publications provide evidence of physiological differences between these neuron types and based on the cellular marker it was found that PV expressing neurons exhibit higher firing rates than Lhx6 and Npas1 neurons. These three constitute the majority of the population of GPe neurons with PV about 55%, Npas1 about 27% and Lhx6 about 30% (Mallet et al.,2012; Hernandez et al.,2015). As Lhx6 is co-expressed either Npas1 or PV, the only two independent neuron types that constitute most of the GPe neuron population are PV and Npas1. Thus, for the remainder of this manuscript, we will consider the PV neurons prototypical and the Npas1 neurons arkypallidal.

Several ion channels have been found to differ among these GPe neuron types. The hyperpolarizing cyclic nucleotide gated (HCN) current may cause an increase in firing rate as this current is known to contribute to spontaneous firing; thus, the larger current in the prototypical neuron would cause a faster firing. The persistent sodium (Nap) current increases the firing rate of the neuron as it maintains a small depolarization. The potassium current inhibits firing; strangely, Kv3 current is smaller in the arkypallidal neuron which would enhance its firing. A difference in input resistance between the two neurons has also been found. The combination of three current differences might be able to account for differences, depending on which effects are stronger.

Another difference between prototypical and arkypallidal neurons is the effect of ethanol. Various studies have also shown that the alcohol influences the large conductance voltage and calcium dependent potassium (BKCa) channel (Kreifeldt et al., 2013; Gouemo & Morad, 2014). The calcium dependent potassium channel (BKCa) plays an important role in controlling the firing rate and are present in the GPe (Song et al., 2010). Ethanol affects the open probability of the BKCa channel (Dopico et al.,1996; Martin et al.2004; Pietzykowski et al., 2004) and its current density is reduced consequent to chronic ethanol exposure (Knott et al., 2002; Piezykowski et al., 2004). The increase in the open probability of the BKCa channel in GPe has been shown to reduce the firing rate of arkypallidal neurons (Abrahao et al.,2016). Despite all this evidence pointing to BKCa as the main mechanism conveying ethanol sensitivity to arkypallidal neurons, other ion channels could be critical. A good method for synthesizing the published data, testing whether other channel changes are needed, and

understanding the effect of ethanol on GPe is by computationally modelling the neuron and simulating the conditions.

There are various ways these GPe neurons are computationally modeled. One approach is the integrate and fire method which uses the following equations $\mathrm{C}\frac{\mathrm{dV}}{\mathrm{dt}} = -K(V - v_r)(V - v_{th}) - u + I$, $\frac{du}{dt} = a(b(V - v_r) - u)$ (Lindahl and Kotaleski, 2016; Lindhal et.al., 2013) where C is the capacitance , V is the membrane potential, v_r and v_{th} are the resting and threshold potentials, I is a current source, K is a parameter determining the steady-state current (I-V) relation, a is the recovery current time constants, b is the voltage dependence of the recovery current and u is the contribution of the neurons slow currents. When the membrane potential (V) reaches V_{Peak} the it is reset and the recovery current is updated. This type of modeling uses a standard conductance-based exponential decay model equation to model static synapses, $\frac{dg}{dt} = -\frac{g}{t_{syn}} + g_0\delta(t - t_{spike})$ where g is the conductance, t_{syn} is the synaptic time constant, g_0 is the maximal conductance for a synaptic event, t_{spike} is the time of the synaptic event and δ is the Dirac delta function (Lindahl and Kotaleski, 2016; Lindhal et.al., 2013). Another way of modeling a neuron is probability-based model, which uses Bayes' theorem and update the probabilities of actions according to the sensory input (Bogacz et al., 2016). This type of modeling is even faster than integrate and fire because it avoids spikes altogether and just model the rate of the neuron. A major drawback of the probability based model is that it is action specific: the firing rate of the model depends on the probability of which action is performed by the animal. Both the integrate and fire method and the probability-based

model are useful to study the network characteristics of the basal ganglia and have been used to simulate the effect of loss of dopamine, which causes a change in firing rate of the GP neuron in Parkinson's disease (Bergman et al., 1994; Nini et al., 1995; Wichmann et al., 1999). However, neither of these models has been used to study the effect of ethanol. Despite their simulation times; these methods of modeling are not useful for understanding how various ion channels control how the neuron behaves. The third approach for neuron modelling is called conductance-based modelling (Evans et.al., 2013; Damodaran et.al.,2013; Griffith et.al., 2016) which uses Hodgkin-Huxley equations for the ion channels (Hodgkin & Huxley 1925a, 1925b). In this method, the firing rate of the neuron is controlled by channel kinetics, synaptic inputs and current injection. In this type of modeling kinetic equation for each type of channel in the neuron is implemented. Conductance-based models have been used to investigate the network characteristics of the basal ganglia. Using the conductance based model we can study how the channel characteristics of the neuron influence its firing properties.

As we are interested in understanding the effect of ethanol on firing rates of GPe, we computationally modeled GPe neurons using a conductance based model. There are several previous conductance based models (Merrison-Hort & Borisyuk, 2013; Günay et.al 2008; Corbit et al., 2016) of GPe neurons that we could have used. These models were rejected either due to only investigating the behavior of a single type of GPe neuron or the characteristics of the GPe neuron in dopamine depleted condition. We could not use any of these models without modifications as they did not include the BKCa channel. In addition, most of these models were published prior to the discovery of arkypallidal

neurons and as a result did not evaluate the difference in channels between prototypical and arkypallidal neurons. Thus, we used one of those models as a starting point (Hendrickson et.al., 2011), and modified it. To create our models and use data reported in literature, we considered the PV neuron the same as the prototypical neuron and the Npas1 neuron the same as the arkypallidal neuron. With an aim of finding the difference between the prototypical and arkypallidal neuron with our model, we tested the PV and Npas1 channel differences reported by Hernandez et.al. (2015) to see if difference in those channels alone are sufficient to explain the difference between prototypical and arkypallidal neurons. We also evaluated whether the effect of ethanol on the calcium dependent potassium channel completely explains the effect of ethanol on the firing rate, or whether additional channels may be involved.

METHODS

We adapted the GP model from Hendrickson (et al., 2011), which was similar to a prototypical neuron, by converting the model which was in Genesis software (http://www.genesis-sim.org/GENESIS/) to MOOSE (https://www.moose.ncbs.res.in). Following, Hendrickson et al. (2011) we modeled all channels using the Hodgkin Huxley framework, which uses the following set of equations to describe current flow:

1. I (V, t) =Gbar*X^p*Y^q*(V-Erev)

2. the gating variable X (and Y) are given by dX/dt =alpha*X – beta*(1-X)

3. the rate constants alpha and beta are dependent on voltage according to

$Rate = \frac{(A+B*V)}{(C+\exp\left(\frac{V_{half}-V}{slope}\right))}$ where A=$\frac{V_{half}}{slope}$ and B= $\frac{1}{slope}$ when C=-1, and A is unconstrained and B=0 when C=0 or +1. The kinetics of the voltage gated calcium (Hva Ca) channel and small conductance calcium activated potassium (SK) channels used in the Hendrickson (et al., 2011) did not adequately match the data (Surmier et al., 1994 and Hirschberg et al., 1999); thus, the rate constants of these channels were updated.

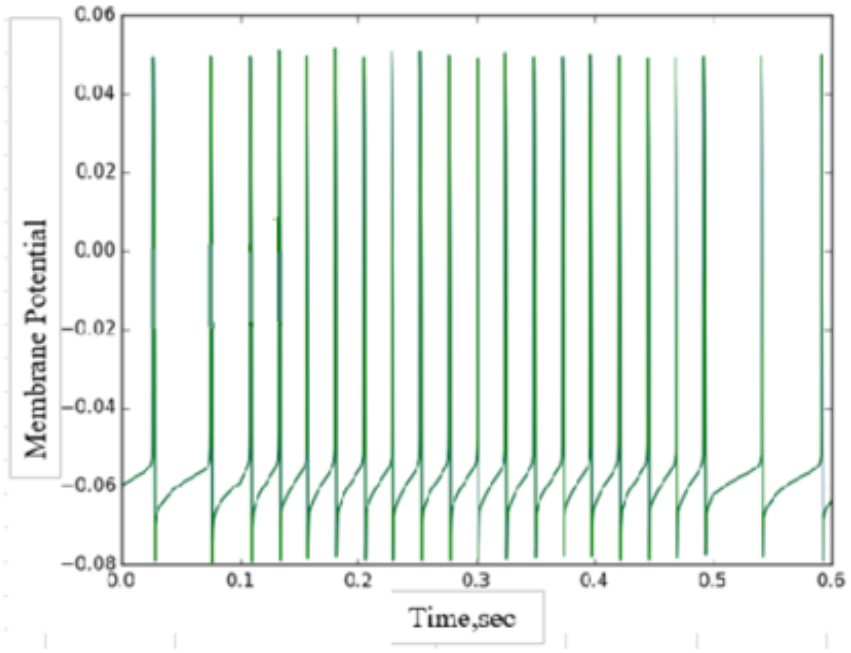
After translating the model from Genesis to Moose, we performed the following steps.

1. We hand tuned the model by changing the conductance value (parameter Gbar in equation 1) for various channels to get spontaneous firing, while matching shape of the action potential(fig.1A).

2.Experiments show that blocking the SK current increases the firing rate of the neuron (Diester et al.2009). Thus, we verified the tuned models by blocking the SK current while simulating somatic current injection of 50 pA and 150 pA (fig1.B). Blocking the SK current did increase the firing rate by 10% for 150pA injection current and 5% at 50pA, which was acceptable as per the data in Diester et al. (2009). With this we considered this model as our Prototypical neuron model.

3. We assumed the constants describing channel kinetics for both the prototypical and arkypallidal neuron were the same, because data in Hernandez (et al., 2015) suggest that the HCN and Nap currents have similar channel kinetics for both prototypical and arkypallidal neuron. Though the other currents might have different channel parameters, for simplicity we considered that the kinetic parameters for both the prototypical and arkypallidal neuron are same. Thus, to create models of the arkypallidal neuron, we only modified the maximal conductance value of the channels to reproduce experimental data, such as firing rate and shape of action potentials (fig2).

A.)



B.)

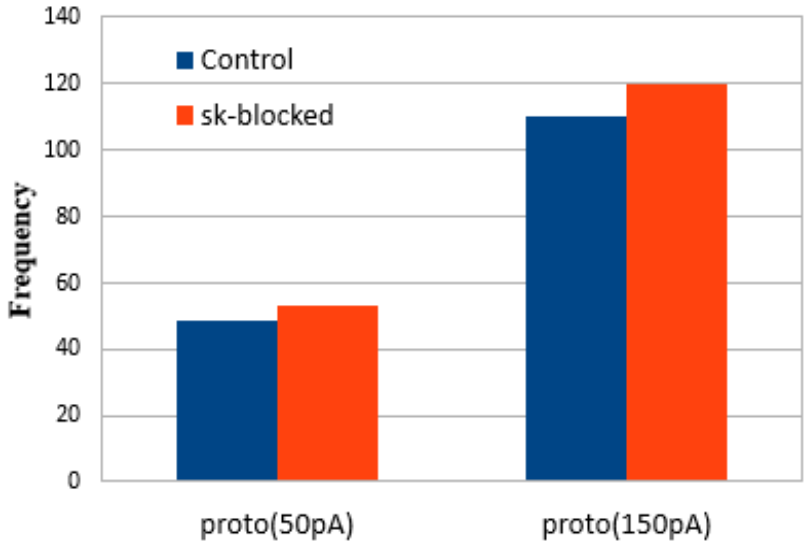


Fig.1 A) Firing of the tuned Prototypical neuron at 25pA current injection. B) Firing rate increases when SK current is blocked, the first panel shows the change in firing rate at 50pA current injection and the second at 150pA current injection.

RESULTS

The input resistance (Rin) of an arkypallidal neuron is higher than the prototypical neuron. While arkypallidal neurons have a greater voltage sag when hyperpolarizing current is injected, prototypical neurons have much less or no voltage sag (Hernandez et al., 2015). To get this difference in voltage sag when a hyperpolarizing current is injected, we found that only decreasing the HCN current for arkypallidal neurons does not give this sag, but this sag can be achieved with a higher input resistance (Rin) (fig3). We made the Rin about 275 MΩ, resulting in a sag ratio of 1.22 which is in the range of the experimental data (Hernandez et al., 2015).

The next step after producing a good response to hyperpolarizing current was to adjust the response to depolarizing current. For a neuron with high Rin the firing rate increased to about 45Hz (fig4) when a 25pA current was injected, which was the opposite response needed. To make an arkypallidal neuron respond to depolarizing current injection, we reduced conductance of the HCN, Nas and Kv4 currents (Hernandez et al. 2015). With only these conductance changes and higher Rin, the firing rate of the neuron increased to 50Hz (fig4) with a current injection of 25pA, which again is too high a firing rate. Note that these conductances do produce a voltage waveform (AHP) for a single action potential that matches recorded data (fig2). Nonetheless, the incorrect firing rate implies that changing the conductance of only these three currents are not sufficient to

explain the difference in firing rate between prototypical and arkypallidal neuron. This result, is not surprising as the lower Kv4 current is known to increase the firing rate of neurons. Our next step was to find what other current differences along with these three current changes are responsible for the difference in the firing rate of the arkypallidal neurons.

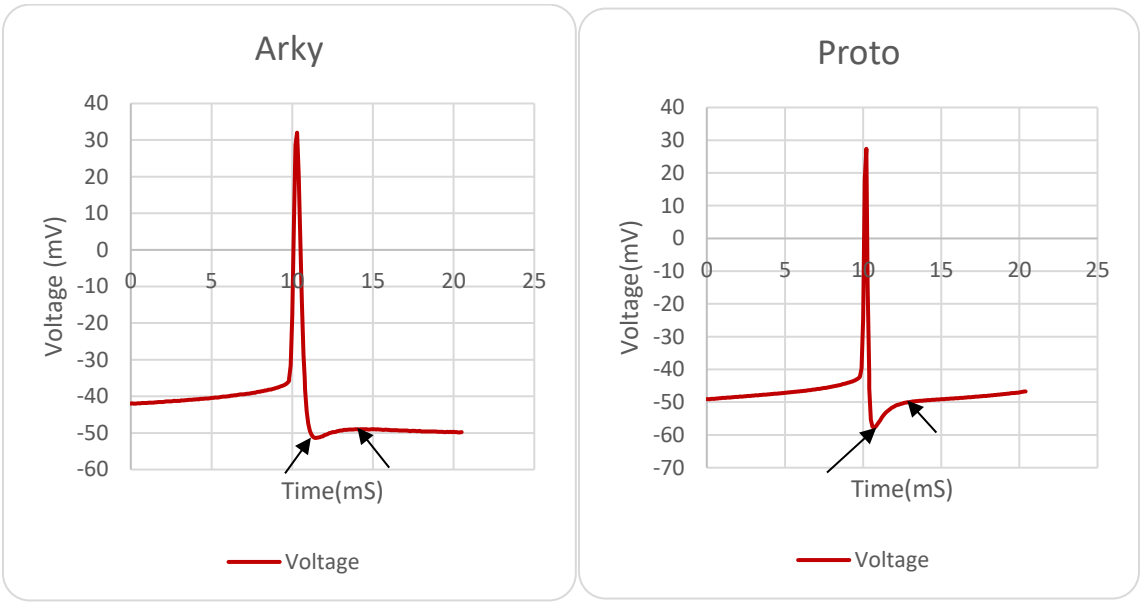
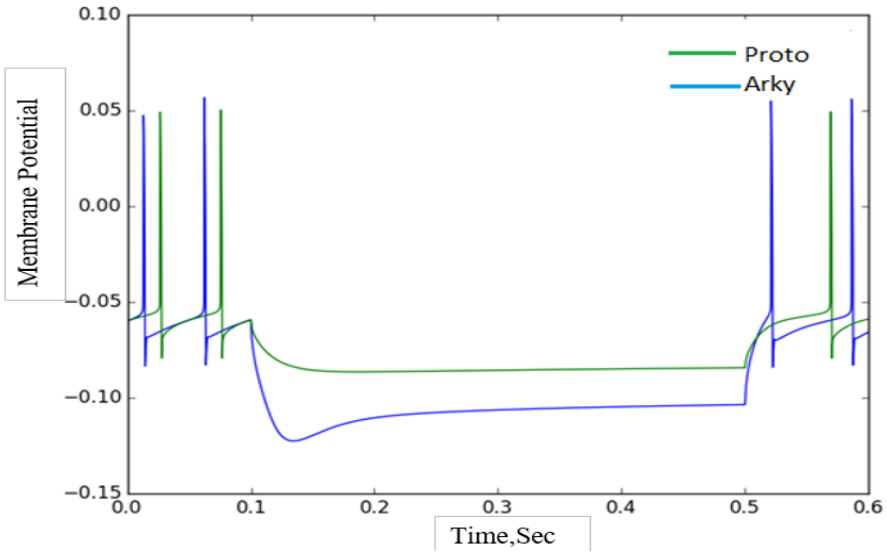


Fig.2) Voltage waveform shape to which the results were compared, the sharpness (or smoothness) of the part marked by arrows (called the AHP) is the focus of waveform.

A.)



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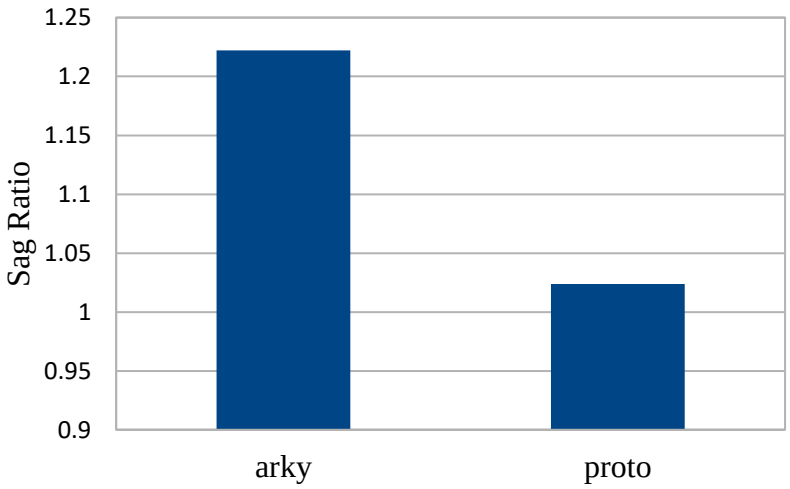


Fig.3 A) The panel shows the neuron behavior at current injection of -160pa, the green line illustrates the response of the prototypical neuron and the blue line is the arkypallidal neuron. B) The panel at the bottom shows the sag ratio of the arkypallidal and the prototypical neuron. This figure shows that the sag ratio for the arkypallidal is higher than the prototypical neuron.

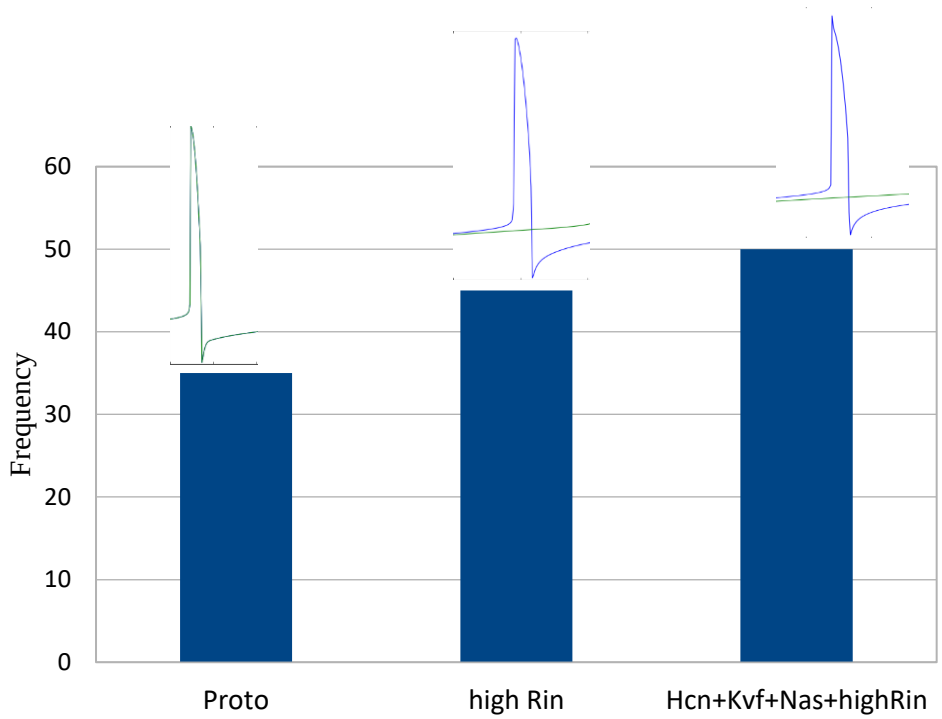


Fig4. Different firing rate between the model with high input resistance and the model with difference in channels as per Hernandez et al. (2015). All columns not labeled as proto are attempted arkypallidal neurons. Waveforms on top of the bars illustrate the action potential shape that was compare with those in Figure 2.

Theoretically increasing the conductance of the BKCa, SK and other potassium currents should reduce the firing rate. Thus, to get a model with low firing rate, we started by changing these currents to get a good arkypallidal neuron model. Increasing only the BKCa current reduces the firing rate to about 25Hz but the voltage waveform (AHP) shape is affected with higher BKCa current (fig5A). Increasing the SK current alone reduces the firing rate to about 32Hz but with higher SK current the AHP shape is affected (fig5A). In other neuron types, the Kv3 current, which has fast dynamics, replaces some of the KDr to allow faster firing (Erisir et al.,1999). We reasoned that the

opposite, replacing Kv3 with KDr, would decrease the firing rate. Indeed, increasing the KDr and reducing Kv3 conductance reduces the firing rate to about 28Hz with a good AHP shape (fig5A). In order to achieve an even lower firing rate with a good AHP shape, in addition to the KDr and Kv3 current changes we also increased the SK current which gave us a firing rate of 25 Hz (fig5A). When we added the change in BKCa current along with these currents changes, the firing rate reduced further to 20 Hz with acceptable AHP shape (fig5A). We blocked the SK current at a current injection of 50pA to check the amount of change in the firing rate of these models, which reveals which of these neuron models is a good arkypallidal neuron. We found that with a blocked SK current, the model with only elevated SK current (and no change to KDr, Kv3 or BKCa) saw an increase of about 50% (fig5B), which is much greater than shown experimentally. The model with the change in SK, KDr, Kv3 and the channels mentioned in the Hernandez et.al. (2015) saw a change of 10% (fig5B), while the model with changes in BKCa, SK, KDr, Kv3 and the channels mentioned in Hernandez (et al., 2015) saw a change of 5% (fig5B), both of which are acceptable changes in firing rate (Diester et al., 2009). Thus, in addition to the currents mentioned by Hernandez (et al., 2015) SK, KDr and Kv3, and possibly BKCa currents are required to establish an arkypallidal neuron with a low firing rate. https://github.com/neurord/spspine/tree/master/moose_nerp/gp all parameters for the model are available here.

A.)

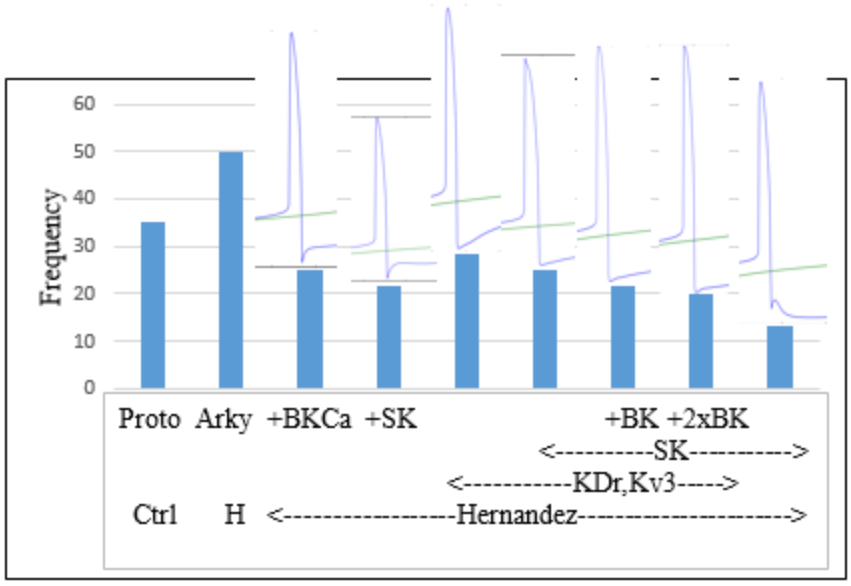
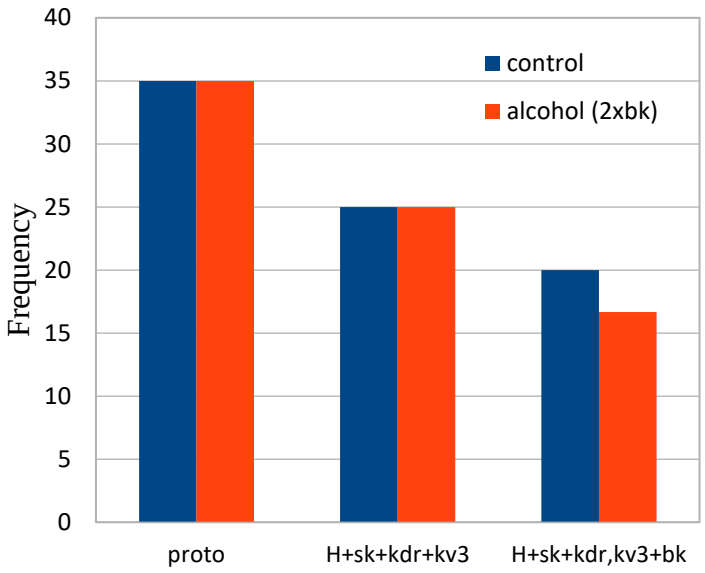


Fig.5A) Shows the different firing rate of all the tested models. The waveforms on the top of the bars illustrate the action potential shape that was compared to Figure 2. B) Shows the change in firing rate of the models at the injection current of 50pA

The next step was to evaluate the effect of alcohol on the neuron model. The model with changes in BKCa, SK, KDr and Kv3 currents and the model with changes in SK, KDR and Kv3 currents (but no change in BKCa) were used to simulate the effect of alcohol as these two models had the lowest firing rates with good AHP shape. To simulate the effect of ethanol we doubled the BKCa conductance, corresponding to the experimentally measured effect on individual BKCa channels. Unsurprisingly, neurons with little BKCa conductance (0.1 Siemens/m^2) did not show any change in the firing rate but the neurons with high BKCa conductance (400 Siemens/m^2) had a lower firing rate (fig6A), suggesting that the sensitivity of other ion channels to ethanol is not required to reproduce the effect of ethanol on firing rate. To confirm these results, we increased the BKCa conductance from 0.1 to either 10.0 or 100.0 Siemens/m^2 for the prototypical neurons, which did not show the effect of ethanol experimentally. With a conductance of 10.0, the firing rate of prototypical neurons was unaffected by ethanol, but with a conductance of 100.0, the firing rate of prototypical neurons was reduced from 35Hz to 30Hz. Using both of these models as our controls, we simulated the effect of ethanol. Doubling the BKCa current further reduced the firing rate of the neuron with the 100.0 (fig7), but not the 10.0 BKCa conductance (fig6B). Thus, we needed a BKCa conductance of at least 10 Siemens/m^2 to see the effect of ethanol on the firing rate, suggesting that prototypical neurons have very little BKCa conductance, ~10.0 Siemens/m^2.

A)



B)

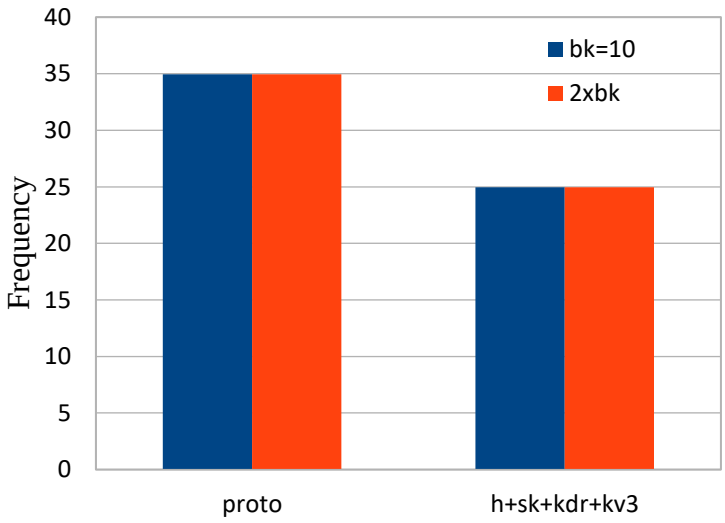


Fig 6. A) Effect of ethanol on the neuron model. Models with higher BKCa current have reduced firing rate in the presence of ethanol. B) Increased the BKCa conductance to 10

Siemens/m^2. No change in firing rate suggest that (i) proto could have higher BKCa current and (ii) arky must have a higher BKCa current

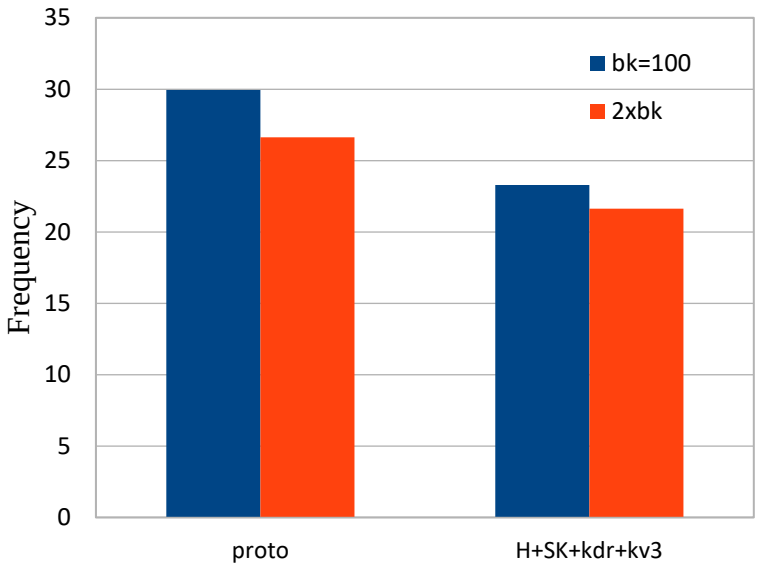


Fig.7) Increased the BKCa conductance to 100 Siemens/m^2. The firing rate reduced in the presence of alcohol suggesting that (i) proto must have a lower BKCa current and (ii) arky must at least match this BKCa current.

CONCLUSION

We computationally modeled a GPe neuron to investigate the difference between prototypical and arkypallidal neurons and the mechanism whereby ethanol modifies firing rate in arkypallidal neurons. Our results suggest that the channels mentioned in the Hernandez et al. (2015) are not sufficient to establish a difference between prototypical and arkypallidal neurons. Channels such as SK, KDr, Kv3 and BKCa are also responsible for the lower firing rate of the arkypallidal neuron. Simulations also led us to the conclusion that the effect of ethanol can be seen on neurons with a high BKCa current.

Our results suggest that there are numerous differences in conductances between arkypallidal and prototypical neurons. Theoretically, increasing any of the (outward) potassium channel conductances should reduce the firing rate. But we found that was not the case, in part because an increased potassium conductance can speed action potential repolarization. To establish a low firing rate neuron, we had to reduce the Kv3 current, which is consistent with the data in Eriser et al. (1999). That paper specifically showed that the fast Kv3 current predominates in fast firing interneurons, and that the fast activation and inactivation cause quick repolarization of the action potential and then a return to basal level quickly allowing the next action potential.

A limitation of our model is that we hand-tuned the model instead of using automatic parameter optimization. The problem with either method of modeling tuning is

that due to numerous non-linarites, the solution most certainly is not unique and likely not optimal. Though automatic parameter optimization is becoming more common (Rumbell et al., 2016; Friedrich et al., 2014; Neymotin et al., 2017), existing algorithms still cannot find ideal matches to data. Part of the problem is due to the high dimensionality of the space, whereas another problem is matching both the waveform and the exact timing of a transient even (spike). Nonetheless, the results should be confirmed with additional model variants, preferably using automatic parameter optimization. Despite these caveats, the prediction that we need lower Kv3 current is likely to be robust based on other models showing high Kv3 current in fast firing neuron (Erisir et al., 1999, Kotaleski et al.,2006). Another caveat of the model is that it uses a "generic" BKCa channel (Evans et al.,2015) i.e., one that as not measured from GP neuron. Thus, an alternative model should be created using a channel with characteristics according to the data present in Song et al. (2010). The main results- that additional differences distinguish arkypallidal from prototypical neurons, and that to a change in BKCa current can account for ethanol induced changes in firing frequency – should be confirmed in the model with alternative BKCa channels.

Most prior GPe neuron models (Hendrickson et al., 2011; Corbit et al., 2016; Merrison-Hort & Borisyuk, 2013; Günay et al., 2008; Ahn et al., 2016) considered only one type of GPe neuron and did not consider all channels. Merrison-Hort & Borisyuk (2013) did not include SK channel in the model, but Diester et al. (2009) showed that the GPe has a SK channel and plays a key role in the firing rate of the neuron. Other models (Hendrickson et al., 2011; Corbit et al., 2016; Merrison-Hort & Borisyuk, 2013; Günay et

al., 2008; Ahn et al., 2016) did not include the BKCa channel in the model. It is likely that some of the models excluded BKCa channel because they were trying to reproduce a prototypical neuron, which may not have much BKCa. On the other hand, Corbit et al. (2016) and Günay et al. (2008) showed that BKCa channel is not required for producing a GPe neuron with a low firing rate low firing rate. Another reason for not considering BKCa channel might be that they were trying to understand the complete basal ganglia network characteristics, rather than the mechanism controlling single neuron firing. Our data shows that we can produce a low firing rate neuron without the BKCa channel but Song et al. (2010) showed that there is a BKCa channel present in the GPe that affects the firing rate of the neuron.

To simulate the effect of alcohol, we added a BKCa channel to our model. With a high BKCa current the firing rate of the neuron reduces. This is insufficient to conclude that the other channels are not affected by ethanol, in part because we did not reproduce the complete range of data (reduction in firing rate) shown by Abrahao et al. (2016). To simulate the complete range, we might need a higher BKCa current but that will affect the shape of the AHP. Alternatively, to suppress a large fraction of firing may require additional ion channels. These possibilities, either arkypallidal neurons have higher BKCa currents or additional currents are changed by ethanol, would be evaluated using neurons that were created with an automatic parameter optimization.

In conclusion, our simulations argue that there are other channels like SK, KDr, Kv3 and BKCa which affect the firing rate of a GPe neuron. After confirming the results using automatic parameter optimization, a network should be created and the effects of

ethanol on the network should be tested Many studies have shown that alcohol affects GABA synaptic connections (Koob, 1998; Koob et al., 1998; June et al., 2003; Criswell et al., 1995) in addition to affecting BKCa channels (Bukiya et al., 2014; Abrahao et al., 2016; Dopico et al., 1996). Making a network model will be useful to evaluate if ethanol's effect on network activity is primarily due to its effect on GABA synapses or BKCa or both the GABA and BKCa and how this in turn affects the overall functionality of the basal ganglia.

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