PROJECT SUMMARY (See instructions):

Rats and mice are the most popular animal models used to study ion channel proteins and circuits in brain neuronal function. This is due to the vast knowledge already obtained in these species and also their ease of use in a laboratory setting. However, striking differences have been identified even between rats and mice and despite the wealth of rodent literature it is currently not known how well the neurophysiology of rodent neurons actually translates to the human brain. It is therefore necessary to directly compare data sets under the same conditions in a number of species to verify that results from rodents reflect functioning of systems comparable with the human brain. The physiology of dopaminergic neurons in the ventral midbrain has not been studied in primates because it is technically difficult and requires the sacrifice of the animal, thus making it prohibitive in species whose individuals are of great value. However, by working with collaborators who are already performing terminal studies on marmosets and baboons we can address this deficiency in the literature without increasing the numbers of these precious species that are currently in use. During the duration of this award we will develop electrophysiological techniques to measure key elements of neuronal function in four species: mouse, rat, marmoset, and baboon. The two primate species (marmoset and baboon) share closer genetic homology with humans and will be used to assess the translatability of work done in rats and mice.

We will focus our efforts on dopaminergic neurons of the substantia nigra because they are responsible for the classic motor symptoms associated with advanced Parkinson's disease, an intractable disease affecting 1% of the human population. We will then use our findings as a stepping stone to future submissions to the national BRAIN initiative investigating this intractable and costly disease. A better understanding of ion channels and neuronal circuits in these neurons is necessary before we can develop treatments that can slow or halt Parkinson's disease progression. Specific experiments will measure signaling in response to a class of neurotransmitter receptors that are coupled to G proteins. Dramatic differences between G protein-coupled receptors have previously been observed between rats and mice, thus these same measures will be used to make comparisons to primate species. G protein coupled receptors are also targets for current Parkinson's disease treatments aimed at symptom relief (such as L-DOPA), thus our findings will be used to inform future hypotheses concerning disease etiology and treatment. The experiments in our first Aim will compare currents mediated by specific channels on dopaminergic neurons and how the currents affect the neuronal electrical activity in brain slices from mice, rats, marmosets, and baboons. The experiments in our second Aim will compare synaptic inputs onto dopaminergic neurons and identify species differences in the mechanisms responsible for synaptic plasticity. At the end of our proposal we expect to have identified key similarities and differences in the neurophysiology of rodents and primates both at the single cell and at the circuit level.

RELEVANCE (See instructions):

This proposal is consistent with the goals of the UT BRAIN seed program as it will establish a new collaboration that will position the investigators for BRAIN initiative funding at a national level. The data collection will be conducted in the labs of Drs. Beckstead (UTHSCSA) and Paladini (UTSA). Co-investigators Drs. Hornsby and Kim (UTHSCSA) have experience with and access to non-human primates and their initial role will be as facilitators toward the physiological studies that we propose. Future submissions will expand on these findings to include primate and rodent models of Parkinson's disease. The UT BRAIN seed program is an ideal mechanism to establish this collaboration because it will *significantly enhance basic and translational investigations into an intractable neurological disease (Parkinson's disease) and will create a line of investigation that will be competitive for funding opportunities in the larger BRAIN initiative.*