Long-Term Depression of Excitatory Inputs to GABAergic Neurons in the Ventral Tegmental Area

Philip J. Sandoval

Brigham Young University - Provo

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Long Term Depression of Excitatory Inputs to GABAergic Neurons in the Ventral Tegmental Area

Philip J. Sandoval

A thesis submitted to the faculty of Brigham Young University in partial fulfillment of the requirements for the degree of Master of Science

Jeffrey G. Edwards, Chair
Scott C. Steffensen
Sterling N. Sudweeks

Department of Physiology and Developmental Biology
Brigham Young University
December 2012

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ABSTRACT

Long Term Depression of Excitatory Inputs to GABAergic Neurons in the Ventral Tegmental Area

Philip J. Sandoval
Department of Physiology and Developmental Biology, BYU
Master of Science

Dopamine cells within the ventral tegmental area of the brain are involved in motivation and reward. Drugs of abuse target these dopamine cells altering their activity and plasticity resulting in addiction. While dopamine cell activity is primarily involved in addiction, the GABA neurons in the VTA have also been shown to have an indirect role. By decreasing the activity of the inhibitory GABA inputs onto dopamine neurons abusive drugs can indirectly increase dopamine cell activity resulting in addictive behaviors. However, although GABA neurons are important in the perception of reward, much less is known about how the excitatory inputs to these cells are regulated and possibly altered by drugs of abuse. Using transgenic mice expressing GFP attached to the GAD promoter, GABA cells were located and patched using whole cell voltage clamp and EPSCs were measured. High frequency stimulation induced LTD of the excitatory inputs to GABA neurons. The endocannabinoid analogue R-methanandamide also induced LTD at these excitatory synapses. These results suggest that endocannabinoids could potentially regulate the activity of GABA cells and as a result the activity of dopamine neurons. The endocannabinoid receptor involved is likely CB1, but not TRPV1 as only the CB1 antagonist AM-251 blocked this high frequency stimulus-induced LTD. Future research could then determine if the pathways involved in this LTD could potentially be altered by drugs of abuse contributing to addiction.

Keywords: VTA, LTD, electrophysiology, endocannabinoid
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INTRODUCTION

Drugs of abuse alter brain function and behavior [1]. Addiction is described as the compulsive need to self-administer drugs in spite of the negative consequences. The common theme among drugs of abuse is that they alter the function of the ventral tegmental area (VTA) of the brain [2]. In order to understand and potentially treat addiction it will be necessary to understand how the VTA is regulated at the synaptic level.

Incentive Salience and Reward Seeking Behaviors

The mesocorticolimbic dopaminergic system of the brain is involved in motivation and reward, and the learning of appetitive behaviors [3]. Rewarding behaviors such as eating, drinking, and sex cause an increase in the levels of dopamine to be released from VTA neurons [3-5]. Animals can be trained to expect a reward in response to environmental cues. When these cues are presented dopamine neurons will increase their firing rate. It is thought that these neurons label rewarding experiences with an “incentive salience” which makes them more desirable than other environmental stimuli [6, 7]. Thus, the VTA of the brain is involved in forming memories of how rewarding and desirable certain behaviors and experiences are.

The way that these memories and drives are expressed is through reward seeking behaviors in animals. The first observation that electrical stimulation of the brain resulted in reward seeking behavior was in 1953. In these experiments it was found that rats preferred to stay in the area of the cage where they had previously received an electrical stimulus to the septal area of the brain [8]. Further brain stimulation studies proposed that the dopamine neurons of the VTA were involved in this conditioned place preference (CPP) [9]. It has recently been demonstrated that selective activation of the dopamine neurons with the VTA is sufficient to induce CPP in mice [10]. In addition to CPP studies animals can also be taught to self-administer
electric stimulation to the VTA. In these paradigms animals are given the opportunity to perform a task that will result in an electric stimulus to the VTA or no stimulus. Animals will actively “seek out” this stimulation by performing the required task to the point of neglecting food or sexual contact [11].

*Cells of the Mesocorticolimbic Dopamine System*

The VTA is part of the mesocorticolimbic dopamine system. The mesocorticolimbic dopamine system consists of the dopaminergic neurons in the VTA which project to both the nucleus accumbens as well as to the prefrontal cortex [12]. In addition to dopamine neurons the VTA also consists of inhibitory GABAergic neurons [13]. These GABA neurons send projections to the nucleus accumbens, the prefrontal cortex, and also synapse locally in order to regulate the activity of dopamine neurons within the VTA [14, 15].

*Neurotransmission and Drugs of Abuse*

The neurotransmitters dopamine and GABA both impact the development of reward seeking behaviors. Dopamine receptor agonists induce CPP and are actively self-administered by rats into the shell of the nucleus accumbens [11, 16, 17]. Dopamine antagonists impair both CPP and the acquisition of self-administering behaviors in response to electric stimulation of the VTA. In addition, rats will actively self-administer GABA antagonists into the VTA and acquisition of this behavior is blocked by pretreatment with dopamine antagonists [11]. Therefore, modulation of GABA neurons provides an indirect mechanism of altering dopamine levels and inducing reward seeking behavior. The common pathway for all drugs of abuse is an increase in the levels of dopamine both within the VTA and its targets [2].

Drugs of abuse can target dopamine neurons themselves promoting increased dopamine release or can act on the GABA neurons within the VTA, decreasing GABA release onto
dopamine neurons resulting in an increase in dopamine release. The influence of drugs of abuse on dopamine release can also be measured behaviorally. Addictive drugs will actively be self-administered into the VTA and induce CPP in rats and mice [11]. These compulsive behaviors are attenuated by pretreatment with dopamine receptor antagonists implicating dopamine in drug seeking behaviors [18]. In addition to elevating dopamine drugs of abuse also alter the plasticity of the synapses that regulate dopamine neurons [12].

**Plasticity**

Synaptic strength can be altered through the neuronal mechanisms of long term potentiation (LTP) and long term depression (LTD). Drugs of abuse “hijack” the natural mechanisms that regulate plasticity at the synapses in the VTA resulting in drug induced forms of LTP and LTD or and inhibition of LTP or LTD [2, 19]. Rat slices that are exposed in vivo to cocaine elicit LTP at excitatory glutamatergic synapses [20]. In addition to altering excitatory inputs to dopamine neurons cocaine has been found to alter the rules that govern the plasticity of inhibitory currents at the dopamine synapses. Rat brain slices that were exposed to cocaine in vivo showed a reduction in their inhibitory GABA currents (I-LTD) at dopamine cells. This results in LTP at the dopamine neurons as a result of the decline in inhibitory current [21]. The endogenously produced endocannabinoid (eCB) 2-arachydonylglycerol (2-AG) is required for the induction of I-LTD in cocaine treated mice implicating eCBs in drug induced synaptic plasticity [22].

**Endocannabinoids**

Endogenously produced eCB molecules regulate the plasticity of synapses within the central nervous system. The regulation of eCB production is characteristic of the location of the synapse although there are common mechanisms shared throughout the nervous system [23].
Cannabinoid synthesis often occurs in the postsynaptic cell usually due to the activation of metabotropic glutamate receptors (mGluR). The two most common cannabinoids produced are 2-arachidonylglycerol (2-AG) and anandamide following typeI mGluR activation. When produced these hydrophobic molecules are able to escape from the postsynaptic cell and either act as a retrograde messenger by activating receptors on the presynaptic axon terminal or by activating receptors on adjacent cells. In the VTA eCBs are involved in the I-LTD described previously. Glutamate release activates mGluRs on the dopamine neurons which activates a PLC and DAG lipase pathway resulting in the production of 2-AG. 2-AG then diffuses across the synaptic cleft and induces I-LTD by activating CB1 receptors on the presynaptic axon terminal [24]. The CB1 receptor has potential as a therapeutic target for drug addiction. Pretreatment of rats with the CB1 receptor antagonist AM-251 reduced methamphetamine intake in rats during self-administration studies [25]. In addition local pretreatment of AM-251 into the nucleus accumbens also attenuated methamphetamine self-administration [26]. In addition to CB1 receptors cannabinoids are also the natural ligands for vanilloid receptors (TRPV1) which could also be of therapeutic interest. In the hippocampus TRPV1 is necessary for the induction of LTD in hippocampal neurons [27]. TRPV1 has also been shown to increase the firing rate of dopamine neurons within the VTA in response to painful stimuli [28].

While eCBs have been implicated in regulating excitatory synapses that modulate dopamine activity much less is known about what regulates the plasticity of excitatory synapses that innervate the GABA neurons within the VTA. Drugs of abuse have the potential to alter the synaptic plasticity of GABA neurons resulting in addictive behaviors. The focus of this project will be on these GABA synapses, how eCBs could potentially modulate them, and how their
plasticity is regulated. This will provide a broader picture of how VTA function is regulated and how addictive behaviors may potentially be treated.

Proposed Research

GABA neurotransmission has been implicated in the behavioral effects of addictive drugs. Animals will actively self-administer GABA receptor antagonists and drugs of abuse have been shown to reduce GABA activity in the VTA [2, 11, 18]. Although modulation of GABA neurotransmission has been implicated in addiction much less is known about how the excitatory neurotransmission that governs GABA cell activity is regulated. Since drugs of abuse act by “hijacking” natural processes that regulate neuronal activity, the first step in understanding how drugs of abuse alter excitatory transmission of GABA cells will be to elucidate the natural mechanisms that alter neurotransmission at these cells. Our data demonstrate that excitatory GABA neurons will undergo LTD in response to high frequency stimulation (Fig 1). A strong candidate for this LTD would be eCB mediated LTD. eCBs have been implicated in promoting LTD in other regions of the brain including the hippocampus, amygdala, as well as to the inhibitory inputs to the VTA [23]. eCBs are an enticing target to study in the VTA as pretreatment with cannabinoid antagonists reduces self-administration of amphetamines in rats [25]. Therefore, the first step in determining eCB regulation of excitatory neurotransmission on GABA cells will be to examine how eCB receptor agonists alter excitatory neurotransmission using electrophysiology.

Drug induced plasticity has also been found to occur at both the excitatory and inhibitory synapse of dopamine neurons altering how LTD and LTP are invoked at these synapses [2, 12]. Much less is known about the plasticity of GABA synapses and if there is potential for drugs of abuse to alter them. In order to understand how drugs of abuse could potentially alter GABA
plasticity it is necessary to first determine the natural plasticity mechanisms present at these synapses.
MATERIALS AND METHODS

Slice Preparation

Mice were carefully cared for in order to minimize pain as completely as possible and to minimize the number of animals used. All procedures followed were in accordance with IACUC guidelines. Mice were anesthetized using isofluorane and decapitated. The brain was quickly removed and horizontal slices 210um thick will be obtained using a vibrotome. Slices were cut in ACSF containing in mM: 220 Sucrose, 3KCl, 1.25 NaH2PO4, 25 NaH2CO3, 12 MgSO4, 10 dextrose, 0.2 CaCl2, saturated with 95% O2/5% CO2 (pH 7.3). After sectioning slices were removed and incubated in ACSF containing 119 NaCl, 26 NaHCO3, 2.5 KCl, 1.0 NaH2PO4, 2.5 CaCl2, 1.3 MgSO4 and 11 dextrose, saturated with 95% O2/5% CO2 (pH 7.4) warmed to 34 C. Slices were incubated for at least one hour before being transferred to the recording chamber [29, 30].

Electrophysiology

When transferred to the recording chamber brain slices were continuously perfused with oxygenated ACSF and warmed to 27-30 °C. Recording electrodes were obtained using a Model P-1000 Flaming/Brown Micropipette Puller. The resistance of recording pipettes were recorded and were kept between the values of 2.1-5Mohms. Recording pipettes were filled with an internal cell solution consisting of in mM: 117 cesium gluconate, 2.8 NaCl, 5 MgCl2, 20 HEPES, 2 ATP-Na1, 0.3 GTP-Na1, and 0.6 EGTA. In all experiments picrotoxin (100uM) were added to the ACSF bath in order to block GABA_A receptors. A bipolar stainless steel stimulating electrode was placed in proximity of fluorescent neurons in order to activate local axon terminals. EPSC’s were invoked at .1Hz with a paired pulse 50ms apart. Fluorescent neurons were patched in whole cell patch mode and clamped at -65mV. EPSC’s were recorded and
amplified using an axoclamp 700B amplifier (axon instruments) low-pass filtered at 5kHz. Amplified EPSC’s were digitally sampled to a PC at 10kHz using a digidata 1440A (Axon Instruments). The input resistance and series resistance were recorded throughout the experiments. If these values change by more than 10% during the experiment it was discarded [30]. GAD-GFP cells were identified using an Olympus USH-1030S fluorescent light source.

Drugs

R-methanandamide, AM251, and Capsezapene were purchased from Tocris Bioscience. AM251 and Capezapene were both dissolved in DMSO while R-methanandamide came predissolved in anhydrous ethanol. Picrotoxin was purchased from Sigma Aldrich and was maintained at 4mM in all experiments in order to isolate excitatory currents.

Analysis of Results

EPSC’s amplitudes were normalized to at least five minutes of baseline before the application of drug to the bath or high frequency stimulation. The five minute average of control EPSC’s right before treatment were then compared to the five minute average of EPSC’s fifteen to twenty minutes post treatment. Significance was examined using a two tailed equal variance t-test (p<0.05).

Statement of Animal Model

CB57 mice expressing GFP on the GAD promoter were used to identify GABA neurons in the VTA. The VTA contains a mixture of both GABA and dopamine neurons and, using these mice, we were able to clearly distinguish between the two cell types and exclusively patch GABA neurons.
RESULTS

High Frequency Stimulation

High frequency stimulation (HFS) has been used to induce changes in plasticity in the hippocampus and in dopamine cells within the VTA and has been associated with natural learning mechanisms [31]. Therefore, we examined plasticity of GABA cells using HFS. While recording from GABAergic VTA cells identified with GFP florescence using whole cell voltage clamp, we determined that high frequency stimulation induced a novel and significant (p<0.016) LTD at excitatory glutamatergic input onto these GABA cells (Figure 1a). Interestingly, it was observed that this LTD could occur in slightly different ways. Most cells responded to the high frequency stimulation by demonstrating a gradual depression of EPSC’s over time (Figure 1b). This occurred in nine out of fourteen cells. However, in two out of fourteen cell’s EPSC’s would initially potentiate to amplitudes greater than control EPSC’s followed by a depression of these same EPSC’s to amplitudes less than the control EPSC’s (Figure 1c).

R-methanandamide

Next, we examined what mediated this novel type of plasticity. As eCBs often mediate LTD we used R-methanandamide, a non hydrolyzable anandamide analogue, which is a known agonist for a variety of eCB receptors such as TRPV1 and CB1 [32]. R-meth (50 uM) was introduced to the bath after a ten minute baseline period. The drug was then washed out after ten minutes to determine if R-methanandamide induces long lasting changes in EPSC amplitude. Exposure to R-methanandamide resulted in LTD of GABA cells which persisted throughout the duration of the experiment (Figure 2, p=0.0014). This suggests that endocannabinoid receptors have the potential to be involved in regulating EPSC amplitude and could be essential for HFS induced LTD of these GABA cells. In order to determine if R-methanandamide activates the
pathways that mediate HFS induced LTD, R-methanandamide was maintained in the bath in order to potentially occlude HFS induced LTD. In the two experiments were performed both cells demonstrated an occlusion of HFS induced LTD (Figure 3), demonstrating that potentially endocannabinoids are involved in the induction of HFS induced LTD as well.

*Capsazapene and AM251*

Two common endocannabinoid receptors in the brain that R-methanandamide could be activating are CB1 receptors and TRPV1 receptors. We wanted to determine whether these receptors are involved in HFS induced LTD. In the presence of TRPV1 antagonist capsazepine (10um) HFS continued to induced LTD in GABAergic VTA cells that persisted throughout the experiment (Figure 4, p=0.01355). This suggests that TRPV1 is not involved in this novel form of plasticity in the VTA. This LTD was not significantly different from control LTD (p=0.788).

As TRPV1 is not apparently involved we next examined the potential role of CB1 receptors in this LTD. We used the CB1 antagonist AM251 and found that there was a trend for AM251 to block HFS induced LTD when comparing it to control LTD experiments (Figure 5, n=5, p=0.602793). Three out of the five cells we experimented on showed no LTD and we are confident that after replicating this experiment a few more times that we would be able to determine significance of this effect suggesting that this novel form of plasticity is mediated by CB1 receptors.
DISCUSSION

**Plasticity**

The synaptic mechanisms of LTD and long term potentiation (LTP) are found throughout the brain. This provides a means for the activity of groups of neurons to be regulated and for an organism to adapt from experience [33]. Plasticity in the VTA is especially important because alteration of dopamine cell activity influences the perception of reward and reward seeking behaviors [2]. In the VTA, HFS can elicit LTP in both the excitatory and inhibitory inputs to dopamine neurons. In addition a low frequency stimulus elicits LTD in the excitatory inputs to dopamine neurons [34]. These mechanisms provide a direct means by which dopamine neuron activity can be regulated and influencing the perception of reward. However, in addition to these mechanisms of plasticity that directly affect dopamine neurons we have demonstrated a mechanism of plasticity that indirectly affects dopamine cell activity by altering GABA cell activity. We have demonstrated a novel form of plasticity in GABA cells which will undergo LTD in response to HFS providing another means by which an organism’s perception of reward can be influenced. In addition it has been shown that drugs of abuse can alter or “hijack” the mechanisms of plasticity changing how they are regulated [35]. This form of LTD could also be altered by drugs of abuse and thus contributing to drug seeking behaviors.

**Endocannabinoids**

Endocannabinoids are primarily involved in the induction of LTD in the various regions of the brain and thus help mediate the processes that help organisms adapt to experience [34, 36]. In the VTA an endocannabinoid pathway is involved in the induction of LTD at both inhibitory inputs and excitatory inputs to dopamine neurons [22, 24]. The induction of LTD at inhibitory synapses (I-LTD) has been found to potentially be important in the effects of cocaine on the
VTA. Normally I-LTD is induced by activation of both mGluR1 and D2 receptors which lead to the formation and release of endocannabinoid molecules which then activate CB1 receptors resulting in I-LTD [24]. The presence of cocaine can “hijack” this pathway through the activation of D2 and mGluRs. This results in the formation of endocannabinoid signaling molecules resulting in a drug induced form of I-LTD [22]. This results in a reduction in the amount of inhibition on dopamine neurons increasing their activity and resulting in an increased perception of reward. Our novel form of LTD could also be regulated by endocannabinoid molecules as we found that R-methanandamide induces LTD at excitatory inputs onto GABA cells. This LTD would have the overall effect of decreasing GABA cell activity which in turn would increase dopamine cell activity. This demonstrates another potential mechanism by which endocannabinoids can regulate the function of the VTA and the perception of reward. There, is also potential for there to be drug induced forms of plasticity at these excitatory inputs providing another means by which endocannabinoids can mediate the effects of drugs of abuse.

TRPV1 and CB1 Receptors

TRPV1 and CB1 receptors have both been found to be involved in the regulation of the VTA. TRPV1 receptors are involved in regulating glutamate release onto dopamine cells and thus influencing the excitability of these cells and dopamine release [28]. We were able to find that our novel form of plasticity, while not mediated by TRPV1, is most likely mediated by CB1 receptors. CB1 receptors have been found to primarily be involved in the mediation of LTD of both excitatory and inhibitory inputs in the VTA [34]. CB1 receptors have also been found to be involved in the expression of reward seeking behaviors. Pretreatment of rats with AM251 reduces the self-administration of amphetamines and has been shown to block the reinstatement of drug seeking behaviors when animals were presented with a cue that was associated with self-
administration of the drug [25, 37]. One potential explanation for this effect is that endocannabinoid antagonists block drug induced forms of plasticity preventing the neural changes that would result in a relapse of behavior.
FUTURE DIRECTIONS

The next step in this research will be to determine if drugs of abuse alter the induction of LTD in these GABA cells. This can be done by injecting mice with cocaine and then determine if HFS induced LTD is occluded or altered in GABA cells. In addition mice could be pretreated with cannabinoid antagonists in addition to cocaine to determine if eCBs are involved in any kind of drug induced plasticity that may be present at the GABA cells in the VTA. By understanding the mechanisms behind HFS induced LTD at GABA cells we will better understand how the activity of dopamine cells can be regulated which influences the perception of reward. We could potentially understand better how drugs of abuse can alter the VTA as a circuit which may contribute to understanding how to treat addictive behaviors.
FIGURE LEGEND

Figure 1a: Averaged experiments demonstrating long term depression of excitatory postsynaptic currents in response to high frequency stimulation (n=14). After obtaining a five to ten minute baseline patched cells were stimulated with high frequency stimulation (HFS) which was given at the arrow. The dashed line represents, in this and other experiments, the mean value of EPSCs before HFS. HFS induced a lasting long term depression (LTD) in GABA cells that persisted throughout the duration of the experiment (p=0.016).

Figure 1b: A single experiment that demonstrates long term depression of EPSC amplitudes in response to high frequency stimulation without the temporary long term potentiation that is seen in figure 1c. HFS was given at the arrow and the cell demonstrated a gradual depression of EPSCs as a result of HFS. Right panel: Average amplitude of thirty EPSCs recorded before HFS (black) and after (red).

Figure 1c: A single experiment that demonstrates a cell whose EPSC amplitudes first undergo a long term potentiation followed by long term depression over time. HFS was induced at the arrow and EPSC amplitude increased initially only to decrease over time to values lower than pre HFS levels. Right panel: Average amplitude of thirty EPSCs recorded before HFS (black) and after (red).

Figure 2: Averaged experiments that demonstrate long term depression of excitatory postsynaptic currents in response to the application of R-methanandamide (50um) to the bath (n=5, p=0.0014). Right panel: example traces from a single experiment illustrating a reduction in EPSC amplitudes. The average amplitude of thirty EPSCs before R-methanandamide exposure (black) and after (red).
Figure 3: Single experiment that demonstrates the occlusion of HFS induced LTD by R-methanandamide. R-methanandamide was maintained at 50um throughout the duration of the experiment. HFS was induced at the arrow and LTD was not observed.

Figure 4: Averaged experiments demonstrating LTD of excitatory inputs to GABA neurons in the presence of the TRPV1 antagonist capsazapene. Capsazepene (10um) was present throughout the experiments and HFS was induced at the arrow resulting the induction of LTD (p=0.01355).

Right Panel:

Figure 5: Averaged experiments where high frequency stimulation (arrow) was given to cells in the presence of AM251 (2um) in order to block CB1 activation. AM251 resulted in a trend of blocking HFS induced LTD (p=0.6).
Figure 1a

Figure 1b
Figure 1c

![Graph showing normalized EPSCs over time.](image)

Figure 2

![Graph showing normalized EPSCs over time with 50um R-methanandamide.](image)
Figure 3

Normalized EPSC vs Time (min)

Figure 4

Normalized EPSC vs Time (Min)
Figure 5
REFERENCES


Curriculum Vitae

Philip J. Sandoval

Contact Information
University of Arizona
Medical Research Building
1656 E. Mabel, Rm 420
Tucson, AZ 85719
(928)-965-1605
sandovap@hotmail.com

Research Interest/Goals:
I am primarily interested in studying the role of synaptic plasticity in addictive behaviors. My goal is to pursue an academic appointment and become a professor where I will run my own lab and have opportunities to teach.

Education:

2010 – 2012 Brigham Young University
Provo, UT
Major: Physiology
Degree: M.S.
Advisor: Jeffrey Edwards
Thesis title: Long Term Depression of Excitatory Inputs onto GABAergic neurons in the Ventral Tegmental Area

2007- 2010 University of Arizona
Tucson, AZ
Major: Physiology
Degree: B.S.

Employment History:

2010-2012 Brigham Young University
Provo, UT
Physiology and Developmental Biology Graduate Program
Research/Teaching Assistant

Awards and Honors:

2012 Research Assistant Awarded, Brigham Young University- Given to exceptional applicants to the department of Physiology and Developmental Biology graduate program. This award was a paid research position for one semester ($5000).

2010-2011 3 Teaching Assistantship Awards, Brigham Young University – Given to exceptional applicants to the department of Physiology and Developmental Biology graduate program. This award was a paid teaching position for three semesters ($15000).

2010 Tuition Scholarship, Brigham Young University- Given to exceptional applicants to the department of Physiology and Developmental Biology graduate program ($4000).
2009  Golden Key International Honor Society- Must be in the top 15% of college class in order to be admitted.

2007  Transfer Academic Scholarship Award- Recipient must have a cumulative college GPA of 3.5 when transferring to the University of Arizona and completed 36 credit hours ($8000).

2006  Presidential Academic Award of Excellence- Awarded to students in the top ten percent of graduating high school class ($10000).

Research Experience:

  2010 – 2012  Physiology and Developmental Biology Graduate Program, Brigham Young University
My time in the Edwards lab helped me to get the research experience I needed to apply for a PhD program. I became very competent in using whole cell voltage clamp to study neural plasticity in the central nervous system. I also learned the basics in writing research proposals which will be helpful as I learn how to write research grants.
Advisor: Jeffrey G. Edwards

Teaching Experience:

  2010-2012  Brigham Young University Department of Physiology and Developmental Biology
PDBio305: Human Physiology lab section (4 semesters, 4 sections/semester, 8hrs/week)
This course gave me opportunities to frequently lecture and interact with students in order to improve my teaching skills. It also helped me to become more comfortable discussing physiology and the basic lab techniques associated with this field such as electrocardiography and sphingonmetry.

Scholarly Presentations:

1. “Addiction and Synaptic Plasticity” Intermountain Graduate Symposium, Utah State University, February 2012.
2. “Long Term Depression of Excitatory Inputs to GABAergic Neurons in the Ventral Tegmental Area” Physiology and Developmental Biology student forum, Brigham Young University, November 2011.