INSENSITIVITY TO PAIN IN SCHIZOPHRENIA: AN EXAMINATION OF SENSORY AND AFFECTIVE PAIN PROCESSING IN AN ANIMAL MODEL

by

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Presented to the Faculty of the Graduate School of

The University of Texas at Arlington in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

THE UNIVERSITY OF TEXAS AT ARLINGTON

May 2009

ACKNOWLEDGEMENTS

Professionally, I would like to thank my committee members, Dr. Cox, Dr. Peng, Dr. Baum, and Dr. Perrotti for assisting me in making this a successful and challenging experience. Thank you to Dr. Peng for helping me to obtain the opportunity to observe at the psychiatric unit at JPS Hospital in Fort Worth. Along those lines, thank you also to Dr. Granado at JPS for allowing me to shadow her and for sharing her experiences in working at the psychiatric unit. I also thank Dr. Odegard for his feedback on a grant that included preliminary data for this experiment. I am truly thankful for the shared knowledge, support, and encouragement of these faculty members, not just on this project. I appreciate NeuroDetective for graciously donating the clozapine used in this study. I thank Chris Hagains for comments on ideas that I had regarding my data. Thank you to Megan Uhelski for coding vials so that I could remain blind, and thank you to Diane Dinh, Matt Davis, and AJ Morris for their assistance in data entry. I especially thank my mentor Dr. Fuchs for providing me with continual guidance and support. I am very fortunate to have such an accommodating and invested mentor. Finally, I thank my husband George Davis and my daughter Bethany for their support in helping me complete this experiment.

March 27, 2009

ABSTRACT

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Patients with schizophrenia have been shown to display decreased sensitivity to pain, which can severely compound the impact of injuries and illnesses. Currently, the reasons for pain insensitivity in this population are unclear. Alterations in both the sensory and affective systems of pain processing have been observed, but the unique contribution of each of these systems has not been elucidated. The aim of this study was to systematically investigate these two components of pain in an animal model of schizophrenia. Animals first underwent L5 spinal nerve ligation surgery in order to provoke a condition of ongoing pain responding. Following recovery from surgery, animals were treated with a combination of 2.58 mg/kg of phencyclidine (PCP), or saline, to induce a condition that parallels human schizophrenia, and 20 mg/kg of the atypical antipsychotic clozapine, or vehicle, in a block design. Responses to mechanical and thermal stimuli were assessed to determine changes in sensory processing, and affective pain processing was examined with the place escape avoidance paradigm. The results showed that animals receiving PCP exhibited decreased sensitivity to mechanical stimulation, and unaltered behavior in the place escape avoidance paradigm. These findings corroborate and strengthen

the human literature investigating schizophrenia and alterations in pain perception. Future directions and implications are discussed.

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CHAPTER 1

INTRODUCTION

Schizophrenia is a debilitating condition that affects approximately 1 percent of the population and is the seventh most costly disorder in the world, with close to 10 percent of all schizophrenia patients committing suicide (Coyle, 2007). Further, 48 percent of patients diagnosed with this disorder receive comorbid diagnoses of drug abuse or dependence (Dixon, 1991). The etiology of schizophrenia is uncertain, but many potential causes have been proposed, including bacterial or viral exposure during gestation (Ozawa et al, 2006), prenatal stress (Lehmann et al, 2000), and genetic predisposition (Bunney et al, 2003). Regardless of the cause, schizophrenia is associated with two interrelated brain changes: decreases in the levels of the excitatory neurotransmitter glutamate in the frontal lobe, a condition labeled as hypofrontality, and dysfunction of the dopamine system, leading to excessive dopamine release in subcortical areas (hyperdopaminergia) (Carlsson and Carlsson, 1990). At this time, it is unclear if hypofrontality leads to hyperdopaminergia, or vice versa, but these conditions have been correlated with schizophrenia symptoms and appear to contribute to disease progression (Carlsson et al, 2000).

People with schizophrenia suffer from a variety of symptoms that can be generally classified into three categories: positive symptoms such as delusions and hallucinations, negative symptoms such as social withdrawal, anhedonia, and avolition, and cognitive symptoms such as decreased working memory (Andreasen et al, 1995). Positive symptoms correlate to excessive dopamine release, whereas negative/cognitive symptoms are associated with hypofrontality (Egerton et al, 2008).

Research and clinical reports indicate that people with schizophrenia also experience a decreased level of pain sensitivity relative to the normal population (Blumensohn et al, 2002;

Davis et al 1979; Dworkin et al, 1993; Dworkin, 1994; Hooley and Delgado, 2001; Murthy et al, 2003). This pain insensitivity results in unreported injuries and wounds, which in turn further increases the fiscal and emotional costs associated with this disorder. For example, Fishbain (1982) described three case reports of patients who presented in emergency rooms with symptoms of severe psychosis and were later diagnosed with schizophrenia. Two to eight days after being admitted for psychiatric care, these patients began to complain of slight pain in various areas of the body. Examinations of these areas revealed a femur fracture, a perforated ulcer which led to the patient's death, and a broken ankle, respectively. These injuries were verified to have occurred prior to hospitalization. Murthy et al (2003) presented a case report on a man with schizophrenia who suffered a tibia fracture but did not report pain as a result of the injury. Others have described similar case reports (Dworkin, 1994).

Based on these case reports, researchers have attempted to better understand schizophrenia-related pain insensitivity. The results of these studies indicate that patients with schizophrenia experience changes in pain perception across a wide array of measurements. Research conducted on schizophrenic patients undergoing surgery for bone fractures showed increased pain perception thresholds, decreased postoperative pain medication, and lower visual analogue scale scores following surgery (Kudoh et al, 2000). Patients with schizophrenia also show increased threshold to thermal stimuli (Jochum et al, 2006), and decreased sensitivity to electrical (Blumesohn et al, 2002; Davis et al, 1979) and mechanical stimulation (Merskey et al, 1962).

Although it is not entirely clear why pain insensitivity may result from schizophrenia, it may be linked to hypofrontality and hyperdopaminergia. In a seminal paper, Olney and Farber (1995) proposed that alterations to the dopamine system could lead to disproportionate suppression of the cortical glutamate system. Glutamate is known to be necessary for pain processing (Chaplan, 1997), and decreases in glutamate would then explain hyposensitivity in patients with schizophrenia. In fact, NMDA receptor antagonists can be used to alleviate

experimentally induced pain, such as inflammatory pain from the injection of formalin (Chaplan, 1997), exposure to warm temperatures (France et al, 1998), and pain from electric shock (McClean et al, 1998). These anatagonists are also effective in treating clinical pain (Ebert, 1998; Price et al, 2000), such as cancer pain (Finkel et al, 2007). Interestingly, the role of the glutamate system in pain insensitivity in schizophrenia has not been greatly explored.

There are issues that obscure the interpretation of clinical and research findings of hyposensitivity to pain in schizophrenia, and therefore need to be further addressed. For instance, it has been shown that antipsychotics used to treat schizophrenia have analgesic properties (Fuchs et al, 1996; Kiser et al, 2001). Although some researchers contend that antipsychotic treatment can not account for the vastness of decreased sensitivity to pain (Dworkin, 1994; Jochum et al, 2006), others state that this possibility should receive more consideration (Fishbain, 1982). Another issue to consider in the literature investigating pain in schizophrenia is of a methodological nature. Dworkin (1994) reviews these issues, pointing to a range of confounds including inconsistencies in the diagnoses criterion for schizophrenia and descriptions of what constitutes pain insensitivity, small sample sizes, and failures to determine if the patients were on medication. Finally, it is unclear if people with schizophrenia have an altered nociceptive system, disallowing them from perceiving pain normally, or if there are changes within brain structures which would alter the affect associated with the perceived pain. (Guieu et al, 1994). This final point is highlighted by the observation that patients with schizophrenia show blunted responses to not only pain, but also other emotions, including pleasure (Potvin and Marchand, 2008). These observations are supported by PET scan and fMRI results from schizophrenia patients which show changes in activation or volume of key brain areas involved in processing emotion (Bar et al, 2002; Wu et al, 1991). For example, studies have found decreased activation in the anterior cingulate cortex (ACC) (Carter et al, 1997; Tamminga et al, 1992), an area of the brain that is heavily involved in processing the affective component of pain (LaGraize et al, 2006). Understanding the role of affect in

schizophrenia may play an important role in further understanding this disease; however, the implications of the findings of altered ACC activation in regards to pain have not been extensively explored in the literature.

These issues need to be further investigated; however, there are ethical and functional complications to studying non-medicated schizophrenic patients. This investigation could be augmented by utilizing an animal model, and several animal models have been used to address many of the behavioral symptoms associated with schizophrenia. For example, increased locomotion in rodent models of schizophrenia is viewed as an indicator of human psychosis, which is a positive symptom of schizophrenia (Marcotte et al, 2001). Alterations in sensorimotor gating, or the ability to filter and appropriate the abundance of environmental stimuli that are encountered by the central nervous system, are a prominent characteristic of schizophrenia (Braff et al, 1978). As such, many animal models of schizophrenia measure sensorimotor gating using a test of prepulse inhibition (Geyer et al, 2001). Deficits in social interaction are also seen in those with schizophrenia, and these deficits have been observed in some animal models (Sams-Dodd, 1995).

Schizophrenia is a complex human condition, and as such, any animal model will not completely parallel the behavioral and neurochemical changes observed in humans. Amphetamine, a dopamine agonist, has been used as a model with some success. For instance, changes in sensorimotor gating and locomotion are a direct result of amphetamine treatment in rodents (Mansbach et al, 1988). However, hyperdopaminergia is thought to be a consequence, not a cause of schizophrenia, and the amphetamine model creates a hyperdopaminergic state. Any validity for this model rests in the reversion of symptoms by other drugs aimed at decreasing dopamine. Therefore, this model lacks construct validity, relies on circular reasoning and provides limited insight into the disorder (Kilts, 2001; Lipska and Weinberger, 2000; Marcotte et al, 2001). Attempts to alter neurological development have also been used. For example, prenatal injections with the antimitotic chemical methylazoxymethanol

acetate produce deficits in sensorimotor gating and impair performance on cognitive tasks (Talamini et al, 1998), but the validity of this model has not been greatly explored (Geyer and Moghaddam, 2002). Neonatal lesions to the ventral hippocampus have also been utilized to model schizophrenia. This model produces several symptoms, including deficits in working memory and social interaction, but these symptoms show limited reversal by antipsychotic drugs, diminishing the predictive validity of this model (Lipska and Weinberger, 2000).

Conversely, the use of phencyclidine (PCP), a hallucinogenic, seems to model schizophrenia well. Phencyclidine is an NMDA receptor antagonist that has gained wide acceptance as a validated animal model of schizophrenia. Depending on the dose and length of time the drug is administered, positive, negative, and cognitive symptoms have been observed (Jentsch and Roth, 1999). Overall, a chronically administered regimen appears to best model the human condition (Jentsch and Roth, 1999), especially the neurological aspects of this disease (Cochran et al, 2003; Jentsch et al, 1998; Egerton et al, 2008). There are several key neurological ways that this model parallels the human condition of schizophrenia including increased subcortical dopamine turnover (Jentch et al, 1998), hypofrontality, decreases in the neuroprotective protein parvalbumin, decreases in glucose utilization in subcortical auditory structures, and decreases in serotonergic binding in the prefrontal cortex (Beasley and Reynolds, 1997; Cochran et al, 2003; Egerton et al, 2008; Morrow et al, 2007; Steward et al, 2004). This model is also associated with low neurotoxicity and has shown validity via the use of antipsychotics in reversing these neurological changes (Egerton et al, 2008). Specifically, the atypical antipsychotic drug clozapine successfully reverses changes in parvalbumin expression (Cochran et al, 2003) and restores cognitive functioning induced by PCP administration (Grayson et al, 2007). Although acutely administered PCP produces many behavioral changes that parallel human symptoms, a chronically administered, low dose regimen of PCP dosing does not fully model some of the behavioral characteristics of schizophrenia, including deficits in social interaction and sensorimotor gating, but it does lead to attentional shift deficits (Egerton

et al, 2008). Further, although cognitive deficits are seen with other models, including acute PCP treatment, deficits seen in response to chronic PCP treatment more closely resemble those seen in humans. For example, acute PCP impairs very basic learning, such as acquisition of a conditioned emotional response, which is intact in schizophrenic patients. Chronic PCP treatment does not alter these “nonspecific” abilities. Further, acute PCP does not seem to lead to the neurochemical and anatomical changes seen in schizophrenia patients (Jentsch and Roth, 1999). Overall, a chronically administered low dose of PCP seems to be the most appropriate means available at this time to model schizophrenia and will be used for this study.

Very few of these models have been used to examine pain insensitivity, and the results of this literature are equivocal. For example, Becker et al (2006) found increases in tail root stimulation thresholds for animals treated with the NMDA receptor antagonist ketamine, but only for singly housed animals. Fiore et al (1999) used prenatal injections of methylazoxymethanol acetate to cause brain abnormalities that are thought to model schizophrenia and reported decreased pain sensitivity. In contrast, Al Amin et al (2004) used neonatal ventral hippocampal lesions to model schizophrenia and found thermal and mechanical hypersensitivity.

Therefore, the aim of this experiment was to determine if changes in pain perception related to schizophrenia are associated with alterations to both the sensory and affective components of pain. Half of all animals underwent a surgical procedure to induce a chronic neuropathic pain state, while the other half underwent a sham procedure. Following recovery from the surgery, animals were randomly assigned to either an experimental or control group with experimental animals exposed to a chronically administered, low dose regimen of PCP and control animals received saline. In addition, during the PCP dosing regimen, half of all experimental and half of all control animals received the atypical antipsychotic agent, clozapine. Seventy two hours following the final dose of PCP, differences in responses to somatosensory testing using mechanical pressure and heat stimuli were assessed. Differences in the affective component of pain were also assessed using an avoidance paradigm. It was hypothesized that

animals with experimentally induced schizophrenia that experience a neuropathic pain state will display decreased sensitivity to both mechanical and thermal stimuli relative to control animals. Further, it was expected that animals in the experimental group would show decreased response to a painful stimulus in the avoidance paradigm relative to control animals, which is indicative of decreased pain affect. It was expected that clozapine treatment would protect against the effects of PCP treatment, and as a result these animals would not behave differentially from control animals.

CHAPTER 2

METHODS

2.1 Subjects

Ninety-six adult Long Evans rats were used for this study. Figure 1 contains a diagram of animal placement with in the study, including the number of animals proposed per group. All animals were singly housed with free access to food and water in a temperature controlled room on a 12 hour light/dark cycle (7am to 7pm). Further, to monitor health and administer the correct amount of drugs, all animals were weighed daily. All procedures were approved by the Institutional Animal Care and Use Committee for the University of Texas at Arlington and adhered to the guidelines set forth by the Committee for Research and Ethical Issues of the International Association for the Study of Pain (Zimmerman, 1983).

2.2 Surgery

A neuropathic pain condition was induced in half of all animals (n=48) by utilizing tight ligation of the L5 spinal nerve. Animals were first anesthetized using isoflurane (3% induction, 2% maintenance) and then were placed in a prone position. The left paraspinal muscles were separated from the spinous process at the L4-S2 levels. The L6 transverse process was then carefully removed with a small rongeur to visually identify the L4-L5 spinal nerves. The L5 spinal nerve was isolated and tightly ligated with 6-0 silk thread. A sham group (n=48) served as a control group and was not ligated. The muscle layer was sutured and the skin incision was closed with wound clips. An antibacterial solution was applied to the surgical site.

For all surgical procedures, the depth of anesthesia was monitored by checking for reflexive behaviors (i.e. eye blink reflex) and by visually monitoring the rate and depth of respiration. Post-surgical signs of infections or overt signs of discomfort were also closely monitored. Animals were allowed to recover for 3 days prior to being exposed to phencyclidine.

2.3 Drugs

Phencyclidine (PCP) (Sigma Aldrich, St. Louis, Missouri) was dissolved in normal saline and injected i.p. at a dosage of 2.58 mg/kg. Control animals received saline in similar volumes. Phencyclidine was given according to the dosing schedule described by Cochran et al (2003). For this protocol, animals were injected once daily for five consecutive days. Injections then occurred three times per week for the next 3 weeks.

The antipsychotic drug clozapine (Sigma Aldrich, St. Louis, Missouri) was dissolved in 2% glacial acetic acid and buffered to a pH of 5.3 to 6.0 using NaOH, and then was given s.c. at a dosage of 20 mg/kg once a day beginning just before the sixth dose of PCP. Control animals received equivalent volumes of vehicle.

2.4 Measurement of the sensory component of pain

2.4.1 Mechanical Paw Withdrawal Threshold (MPWT)

To measure mechanical threshold levels, animals were placed within a Plexiglas enclosure (20x10.5x40.5 cm) and allowed to habituate for 15 min. The enclosure was positioned on top of a mesh screen in order to administer mechanical stimuli to the plantar surface of both hind paws. Using the up/down method proposed by Dixon (1980), mechanical threshold measurements for each hind paw were obtained. For this procedure, eight von Frey monofilaments (4, 6, 10, 20, 39, 78, 142, and 239 mN) were utilized in the following manner. Each trial began with a von Frey force of 10 mN delivered to the right hind paw for approximately 1 s, and then the left hind paw. If there was no withdrawal response, the next higher force was delivered. If there is a response, the next lower force was delivered. This procedure was performed until no response was made at the highest force (239 mN) or until four stimuli were administered following the initial response. The paw withdrawal threshold for each paw was calculated using the following formula: [Xth] log = [vFr] log + ky, where [vFr] is the force of the last von Frey used, k =0.2492 and is the average interval (in log units) between the von Frey monofilaments, and y is a value that depends upon the pattern of withdrawal responses. If an animal did not respond to the highest von Frey monofilament (239 mN), then y

=1.00, and the mechanical paw withdrawal response for that paw was calculated to be 424.30 mN. Mechanical paw withdrawal threshold testing was performed across three trials, and the withdrawal values were averaged over these trials to determine the mean mechanical paw withdrawal threshold for each animal. Any animal that failed to display significant changes in MPWT responding, deemed in this experiment to be a 50% decrease from baseline scores, was not included in the experiment.

2.4.2 Thermal latencies

Following completion of MPWT measurement, animals were moved to a Plexiglas chamber (Plantar Test [Hargreaves's Apparatus], Ugo Basile, Schwenksville, PA) and habituated for 15 minutes prior to thermal testing. To measure thermal latencies, a thermal stimulus was applied to the plantar surface of the left and right hind paws, and the latency for the animal to withdraw from the stimulus was measured. Once the animal moved the paw, the heat source was automatically terminated. If the animal failed to withdraw the paw within 20 seconds, the stimulus was terminated to avoid any damage to the skin. Thermal measurements were taken for three trials and then averaged across all trials for both paws. Once thermal measurements were completed, animals were allowed to rest for approximately 20 minutes before being tested for prepulse inhibition.

2.5 Measurement of the affective component of pain

2.5.1 Place escape avoidance paradigm (PEAP)

On day 32, animals were tested in the place escape avoidance paradigm (PEAP). The paradigm consists of a 60x30x30 cm Plexiglas chamber, half of which is painted white (light side) and half is painted black (dark side), positioned on a wire mesh stand that is 30 cm off the table surface. During the 30 minute testing session, animals were allowed unrestricted access to both sides of the chamber. Testing began immediately by applying suprathreshold mechanical stimulation (476 mN von Frey monofilament) to the plantar surface of the hindpaws every 15 seconds. If the animal was in the preferred dark side of the chamber at the 15 second interval, the hind paw ipsilateral to L5 ligation was stimulated; if the animal was in the non-

preferred light side of the chamber, the hind paw contralateral to injury was stimulated. The experimenter recorded where the animal was located during stimulation as well as the number of times the animal crossed from the light to dark sides during the 15 second interval, and upon testing completion, found the mean percentage of time spent in each side of the chamber. The PEAP test has been utilized extensively to study the affective component of pain and the role of the anterior cingulate cortex in pain processing (LaBuda and Fuchs, 2000 & 2005; LaGraize et al, 2004 & 2006).

2.6 Measurement of prepulse inhibition (PPI)

PPI testing, which is a measure of sensorimotor gating, was performed using the Startle Monitor Behavioral Testing System (Hamilton Kinder, Poway, CA). Following a 5 minute acclimation period, animals were exposed to a background stimulus of 70 decibels (dB). This background noise remained constant during testing. There were 8 trial types, administered in a random manner and separated by an average inter trial interval of 15 seconds. The following trial types were used: a single 40 ms burst of a 120 dB noise (PULSE ONLY); three trial types of the presentation of the prepulse tones only (4, 6, or 8 dB above the background noise); a trial which contains only the background noise (NO STIMULUS); and three prepulse trials. For the prepulse trials, the trial began with a noise that is 4, 6, or 8 dB above the background noise. This prepulse tone was presented for 20 ms, after which the chamber returned to background noise level. One hundred ms later, a 120 dB noise was presented for 40 ms. The entire session lasted approximately 20 minutes. To calculate the percent prepulse inhibition, each animal's response was calculated for the three prepulse trials separately according to the following formula: (startle amplitude on PULSE ONLY trials – startle amplitude on prepulse trials) / (startle amplitude on PULSE ONLY trials) * 100.

2.7 Procedures

Figure 2 outlines the procedures. On Day 0, baseline measurements were obtained for MPWT, thermal, and PPI. The next day (Day 1), animals underwent L5 ligation surgery and were then allowed to recover for the following three days. On Day 4, animals were again tested

for MPWT, thermal, and PPI responding. Immediately following this testing, animals received the first injection of PCP, or saline. Phencyclidine injections then occurred on Days 5-8, and Days 11, 13, 15, 18, 20, 22, 25, 27, and 29. Ten minutes following the PCP injection on Day 8, animals were tested for changes in PPI. This test time was chosen based on literature demonstrating acute PCP effects on PPI (Egerton et al, 2008). Beginning just prior to the PCP injection on Day 11, animals were injected with clozapine, or vehicle. Antipsychotic treatment then occurred daily until Day 29. Following the final injection of PCP, animals were withdrawn from the drug for 72 hours (Cochran et al, 2003). On Day 32, MPWT, thermal, PPI, and PEAP testing occurred.

2.8 Data analysis

Data were analyzed with a repeated measures mixed analysis of variance (ANOVA) for each of the dependent variables (mechanical paw withdrawal threshold testing, thermal threshold testing, place escape avoidance paradigm testing, prepulse inhibition, and weight) using time as the repeated measure and surgery (sham, surgery), condition (saline, PCP), and drug (vehicle, clozapine) as the independent variables. For analysis of prepulse inhibition, the independent variable of decibel (70+4, 70+8, 70+12) was added to the above measures. Significant effects were further examined using the Tukey HSD test for post hoc comparisons. The significance level was set at $p<.05$ for all tests.

CHAPTER 3

RESULTS

3.1 Sensory threshold testing

3.1.1 Mechanical Paw Withdrawal Threshold (MPWT)

Analyses revealed a significant main effect for surgery ($F(1, 88) = 228.83$; $p<.001$), condition ($F(1, 88) = 5.30$; $p<.05$), and drug ($F(1, 88) = 10.32$; $p<.01$), as well as significant interactions (Figure 2). A significant time X surgery interaction was found ($F(2, 176) = 150.38$; $p<.001$). Post hoc analyses indicated that L5 ligation surgery induced significant sensitivity to mechanical stimulation when measured on Day 4 ($p<.001$), and this sensitivity remained on Day 32 ($p<.001$). A significant time X drug interaction was also found ($F(2, 176) = 11.11$; $p<.001$), and post hoc analyses indicated that clozapine rats were more sensitive to mechanical stimulation on Day 32 ($p<.001$). Importantly however, a significant time X condition interaction was found ($F(2, 176) = 3.36$; $p<.05$), with post hoc analyses showing that animals treated with PCP showed less sensitivity to mechanical stimulation on Day 32 ($p<.05$).

3.1.2 Thermal latencies

Unlike the findings for mechanical testing, main effects were not found for condition or drug for thermal threshold testing (Figure 3). A significant main effect for surgery ($F(1, 88) = 5.64$; $p<.05$) and a significant time X surgery interaction ($F(2, 176) = 11.38$; $p<.001$) were found. Post hoc analyses revealed that surgery induced a significant sensitivity to thermal stimulation on Day 4 ($p<.001$), but that sensitivity was diminished by Day 32 ($p>.05$).

3.2 Affective testing

3.2.1 Place escape avoidance paradigm (PEAP)

The analyses for the place escape avoidance paradigm revealed a significant main effect for surgery ($F(1, 88) = 5.57$; $p<.05$) and a significant time X surgery interaction ($F(5, 440)$

= 5.61; p<.001). Overall, surgery animals spent more time in the light side of the chamber than sham animals, and PCP and clozapine treatment did not alter this (Figure 4).

3.3 Prepulse inhibition testing

For prepulse inhibition (Figure 5), a significant main effect was found for decibel level (F (2, 264) = 76.06; p<.001), as well as a significant time X decibel level interaction (F (6, 792) = 2.20; p<.05). Post hoc analyses indicated that the percentage of prepulse inhibition was greatest for the 70+12 decibel level (p<.001), followed by the 70+8 (p<.001) and 70+4 (p<.001) decibel levels, respectively. No significant effects were found for surgery, condition, or drug.

3.4 Weight

The analysis for weight revealed a significant time X drug interaction (F (2, 176) = 38.93; p<.001), with post hoc tests showing no significant baseline differences between clozapine and vehicle treated animals (p>.05). Clozapine rats did, however, gain significantly less weight than vehicle treated animals by Day 32 (p<.001). No significant effects were found for surgery or condition (Figure 6).

CHAPTER 4

DISCUSSION

This experiment was the first to examine altered nociception using the PCP model of schizophrenia, and the first to investigate the affective aspect of pain in any model of schizophrenia. The major findings of this study were that 1) animals exposed to PCP experienced the expected decrease in sensitivity to mechanical stimuli, indicating altered processing of the sensory component of pain, and 2) PCP treated animals did not show altered responding during the place escape avoidance paradigm, indicating that the affective component of pain was unaltered.

The discovery of decreased sensitivity to mechanical stimulation for animals treated with PCP is an exciting finding that supports the observation of decreased pain sensitivity in humans. For example, Merskey et al (1962) applied mechanical pressure, using an algometer, to the tibia of schizophrenic patients and found that “movement withdrawal” (i.e. no withdrawal, slight or moderate withdrawal, or complete withdrawal of the stimulated area) was hampered in this population. Potvin and Marchand (2008) conducted a meta-analysis of twelve published articles investigating the phenomenon of pain insensitivity, taking into account the type of stimulation (i.e. thermal, electrical, or mechanical) and the exact measure used, the state of the patient (inpatient versus outpatient), and the number of subjects. Overall, their results supported the findings of decreased response to pain in those with schizophrenia. Therefore, the finding of the current study provides strength to the use of chronically administered PCP in investigating pain and schizophrenia, and opens the door for translational research on this topic.

While the finding of decreased sensitivity to mechanical stimulation is interesting and in-line with the hypothesized results, the lack of expected deficits in PPI potentially calls to

question the validity of these results. Humans with schizophrenia have been reported to display decrements in sensorimotor gating, and the validity of any model of schizophrenia is often assessed by testing for these deficits (Geyer et al, 2001). Researchers examining PPI following chronic exposure to PCP often fail to find alterations in sensorimotor gating (Geyer et al, 2001). This finding remains regardless of the amount of time PCP is administered. Martinez et al (1999) tested for PPI deficits following PCP dosing everyday for 5 or 14 days (Martinez et al, 1999), and Egerton et al (2008) failed to find PCP related PPI changes following a 30 day chronic dosing regimen. Currently, only one study has found decrements in PPI following chronic exposure to PCP, and decrements were only observed when PCP was administered both postnatally and during adolescence (Rasmussen et al, 2007). The results of this study, along with preliminary results from our laboratory (unpublished data), confirm that chronic PCP treatment does not produce decrements in PPI. However, acute effects of PCP were also not observed in this study. This finding is surprising, given the normally robust effects of acutely administered PCP on PPI found in our lab (unpublished data) and by other researchers using rodents (Bakshi and Geyer, 1995; Jentsch and Roth, 1999; Morris et al, 2005; Mansbach and Geyer, 1988) and primates (Linn and Javitt, 2001). For all of these studies, testing of PPI occurred 10 minutes following PCP treatment, just as it did in the present study. Unfortunately, the reason for a lack of PCP-induced deficits on PPI is completely unclear at this time. Other researchers have noted or heard reports of “lost” PCP effects, but this generally occurs over several generations of animals exposed to the same PPI parameters (M Rutledge, personal communication, February 19, 2009; M Kinder, personal communication, February 26, 2009), which is not the case in this experiment.

Another unexpected finding was the lack of effect of PCP on thermal sensitivity. While L5 ligation surgery did produce a significant decrease in thermal latencies, as can be seen on Day 4 in figure 3, this sensitivity was diminished by Day 32 for all animals. Using the L5 ligation model, Kim and Chung (1992) showed that thermal hypersensitivity continued for 35 days post

surgery; however, the time course of thermal versus mechanical hypersensitivity has not been extensively explored. Hao et al (2005) studied thermal and mechanical responding as a result of L5 ligation and found that, while mechanical sensitivity lasted for up to eight weeks, thermal responding had begun to recover three weeks post surgery. Because thermal sensitivity had resolved by testing time on Day 32, it is difficult to detect the effects of PCP or clozapine treatment on thermal responding in this experiment.

The results for the place escape avoidance paradigm suggest that PCP treatment did not alter the affective component of pain. Instead, it was found that animals in the pain condition spent more time in the light side of the chamber, regardless of drug treatment. A re-examination of the human literature reveals interesting corroboration for the findings of this study. The signal detection theory, described extensively by Clark (1971), purports to measure sensory discrimination (d'), which could be seen as a parallel to the MPWT measurement in this study, and affective pain processing (the response criterion), which is captured here with the place escape avoidance paradigm. Using this theory to investigate pain in schizophrenia, Dworkin (1993) found that "patients with schizophrenia have poorer sensory discrimination of painful stimuli [compared to control subjects] but do not differ…with respect to their response criterion for reports of painfulness." The results of this study support the findings of Dworkin and show decreased sensory responding and unaltered pain affect for the PCP group. Jochum et al (2006) suggest that this combination of increased thresholds for pain along with similar responses to a stimulus that is perceived as painful reflects an executive function problem, not necessarily a somatosensory issue.

The ACC is involved in processing the affective component of pain (LaGraize et al, 2004). Based on the findings in the human literature of structural changes in the ACC (Tamminga et al, 2000), it was expected that pain affect would be altered for the PCP group, but this effect was not found. The reason for this apparent discrepancy may involve the functional arrangement of the ACC. Devinsky et al (1995) discussed the anatomical and functional

divisions of the ACC, with certain areas being heavily involved in affect (25, 33, and rostral area 24) and others areas being involved in cognition (caudal areas 24 and 32). The results of the current study indicate that the area(s) of the ACC involved in determining the response to pain may not be as heavily taxed as the area(s) involved in making the discrimination as to what is painful. This would suggest that the more rostral areas of the ACC are not primarily altered, as demonstrated by normal place escape avoidance behavior. Instead, it may be that the projections of the more caudal areas are disrupted. For instance, the concordant effects of schizophrenia on the dorsolateral prefrontal cortex (DLPFC), which is necessary for attention switching (Vanderhasselt et al, 2006), along with changes in ACC function, may play an important role in moving attention from a current task or area of focus to a painful stimulus. Indeed, research shows that the excitatory ACC/DLPFC projections have decreased glutamate, which could produce NMDA receptor hypofunction. This in turn can lead to compensatory increases in glutamate transmission at nearby non-NMDA glutamate receptors, causing neurotoxic effects that produce widespread apoptosis, creating the observed decreases in ACC and DLPFC grey matter volume (Fornito et al, 2008). Ultimately, these changes could alter the function of the ACC/DLPFC pathway, leading to problems in attentional switching and discrimination resolution.

At this point, more research needs to be conducted to determine if a somatosensory deficit can partially account for the changes in pain sensitivity in those with schizophrenia. Researchers using electroencephalograph (EEG) have found alterations in event-related potentials in the brains of patients with schizophrenia (Fallgatter, 2001), but it would be beneficial to examine the changes in spinal processing as well. For obvious ethical reasons, invasive cellular electrophysiology has not been conducted on humans with schizophrenia. At this point, this method has also not been utilized in animals due to the lack of an adequate model of pain insensitivity in schizophrenia. Based on the findings of this study, it is now

possible to begin to explore and juxtapose supraspinal processes, such as executive function, to spinally mediated changes that occur within the pain system for those with schizophrenia.

Finally, it was hypothesized that treatment with the antipsychotic agent clozapine would reverse the effects of PCP exposure. For example, it was expected that surgery animals receiving both PCP and clozapine would behave similarly to surgery animals receiving saline. Instead, none of the dependent variables revealed a significant PCP/clozapine interaction. For MPWT testing, clozapine was found to induce mechanical sensitivity. Further, animals receiving clozapine displayed significantly less weight gain than vehicle treated rats across the time course of the experiment. Case studies have reported that treatment with clozapine provides pain relief and aids in obtaining restful sleep (Karp et al, 1999), and at least one animal study has shown robust antinociception, hypothesized to be a result of activation of the opioid system, from a single dose of 30mg/kg of clozapine (Schreiber et al, 1999). On the contrary, chronic treatment with clozapine has been associated with deleterious, and painful, side effects including recurrent pancreatitis (Chengappa et al, 1995), pericardial effusion (Boot et al, 2003), cardiomyopathy (Phan et al, 2002), bowel obstruction, and constipation (Tang and Ungvari, 2008). Due to the dangerous side effects of clozapine, its use as an analgesic in the general population is limited. In animal studies, clozapine is generally not administered chronically, and these few studies have not examined pain processing. As a result, the mechanisms of the hypersensitivity reported here have not been examined but provide an interesting avenue for future study.

In conclusion, the results of this study show decreased sensitivity to mechanical stimulation and unaltered affective pain responding in an animal model of schizophrenia. This is the first animal study to examine both the sensory and affective components of pain, and exploring these systems of pain is a needed step in understanding why patients fail to report painful and deleterious conditions. Greater insight into this condition may provide broader knowledge of schizophrenia etiology and disease course and treatment. This in turn will

ultimately lead to a significant improvement in clinical outcomes for those diagnosed with schizophrenia.

APPENDIX A

FIGURES

Model	Treatment	Surgery	
		Ligation	Sham
PCP	Clozapine	n=12	n=12
	Vehicle	n=12	n=12
Saline	Clozapine	n=12	n=12
	Vehicle	n=12	n=12

Figure 1 A diagram of group designation

Day 0: Test for MPWT, thermal, and PPI baseline values
↓
Day 1: Surgery (half will receive L5 spinal nerve
ligation; half will undergo a sham procedure); Followed by 3 days of recovery
↓
Day 4: Test for MPWT, thermal, and PPI changes as a result of the surgery; Inject PCP
↓
Days 5-7: Inject PCP
↓
Day 8: Inject PCP; Conduct PPI testing
↓
Days 9 & 10: Rest
↓
Day 11: Inject clozapine; inject PCP
↓
Days 12-29: Inject clozapine daily
↓
Days 13, 15, 18, 20, 22, 25, 27, &29: Inject clozapine; inject PCP
↓
Days 30 & 31: PCP withdrawal
↓
Day 32: Test for MPWT, thermal, and PPI changes; Conduct PEAP testing

Figure 2 Outline of procedures

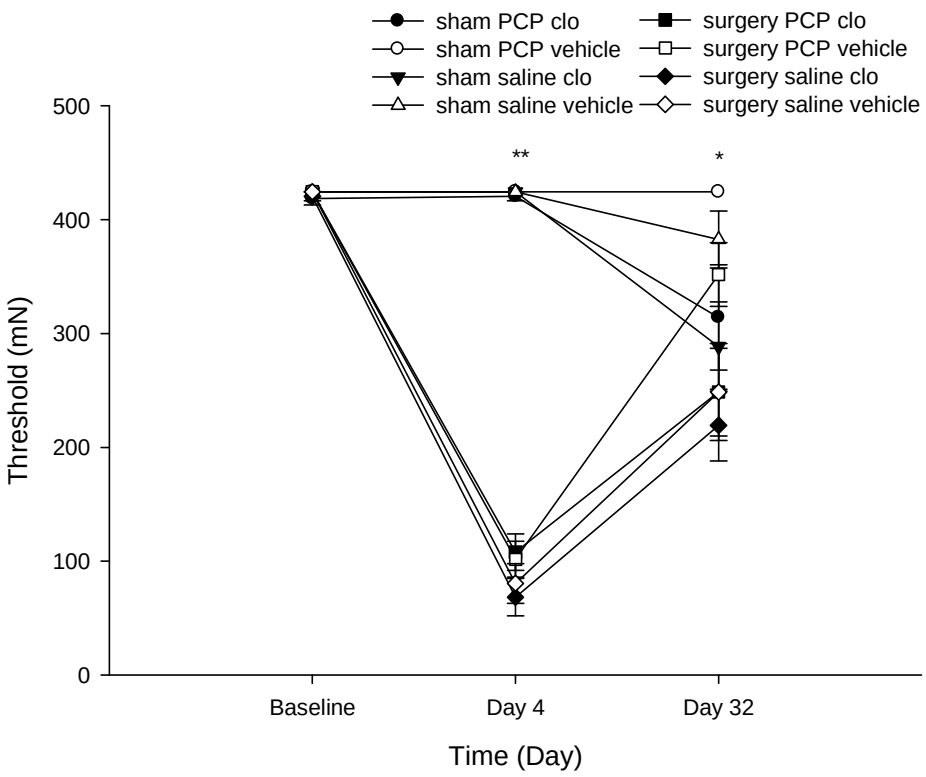

Figure 3 Mechanical paw withdrawal threshold

Mean (+/- SEM) mechanical paw withdrawal thresholds (MPWT) for all animals (n=12). Twenty four hours following baseline measurement of MPWT, animals underwent L5 spinal nerve ligation or a sham procedure. Following recovery from surgery, animals were again tested for MPWT on Day 4. As can be seen, L5 ligation induced a significant decrease in thresholds to mechanical stimulation compared to sham animals. Beginning on Day 4, animals were administered phencyclidine (PCP), with the addition of clozapine (clo) starting on Day 11. Animals were tested for MPWT a final time on Day 32. On this test day, PCP treated animals showed less sensitivity to mechanical stimulation compared to saline treated animals. Further, clozapine treated animals had increased sensitivity compared to vehicle treated animals on this test day. *=p<.05; **p<.01

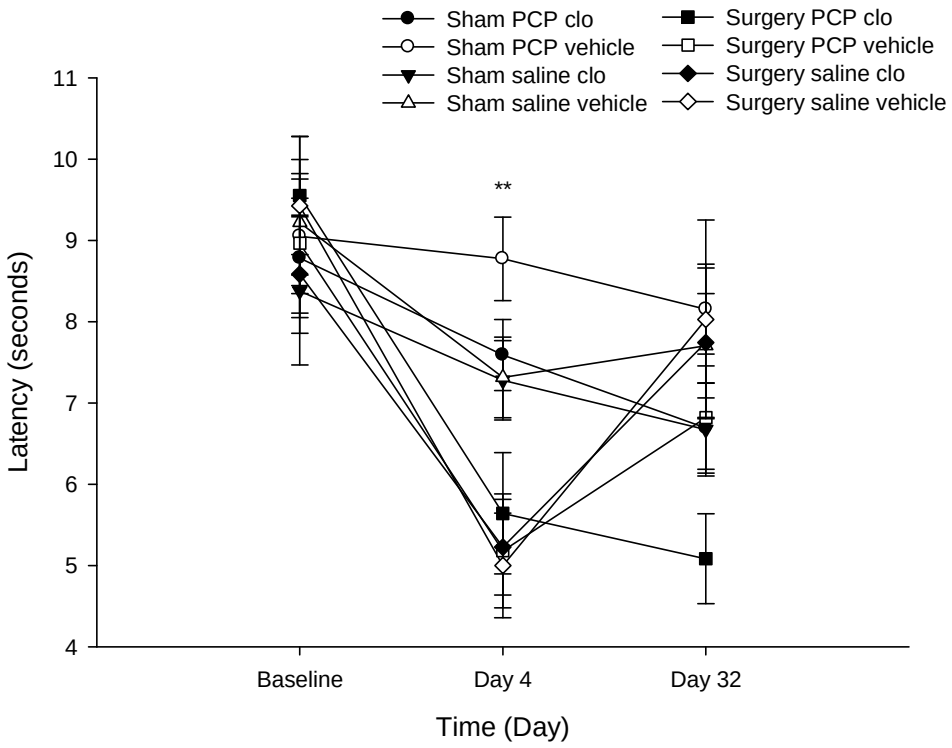

Figure 4 Thermal latencies

Mean (+/- SEM) thermal latencies for all animals (n=12). The testing protocol for thermal latencies was similar to testing for MPWT testing. On Day 4, thermal latencies were lower for L5 ligated animals compared to sham animals. On Day 32, the effect of surgery on thermal latencies was no longer significant. No effects for PCP or clo were obtained. **p<.01

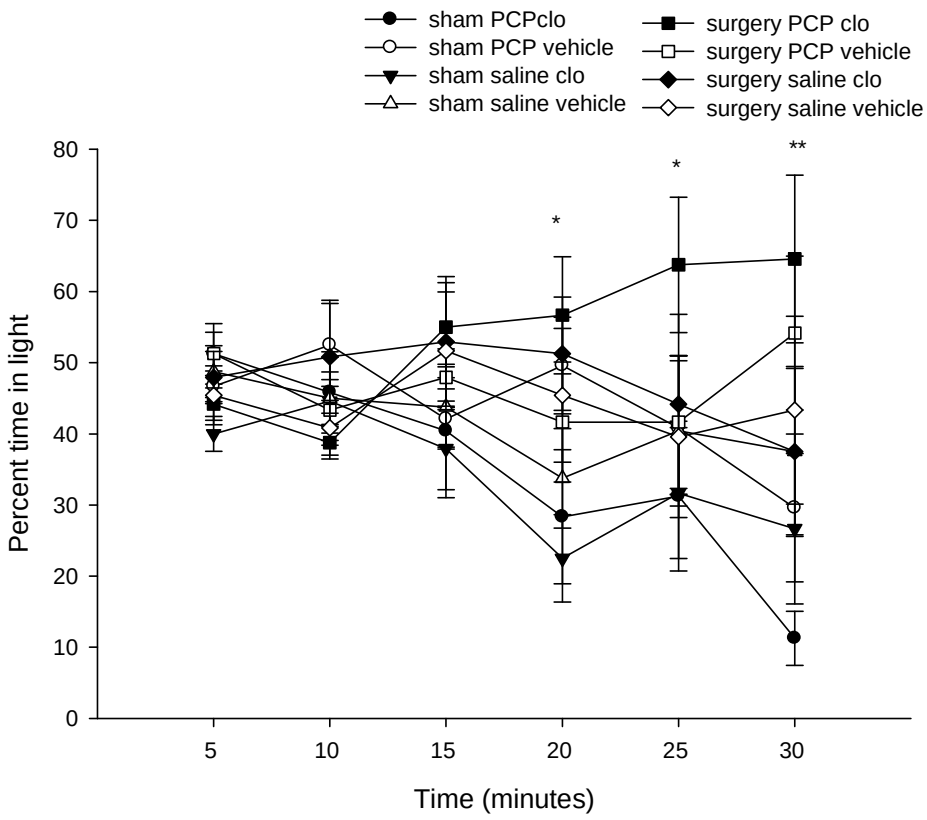

Figure 5 Place escape avoidance paradigm

Mean (+/- SEM) percentage of time spent in the light side of the chamber during the 30 minute place escape avoidance paradigm test for all animals (n=12). Testing occurred on Day 32 following all other behavioral data collection. Animals receiving L5 spinal nerve ligation spent significantly more time in the light side of the chamber compared to control animals at the 20, 25, and 30 minute time points. *=p<.05; **p<.01

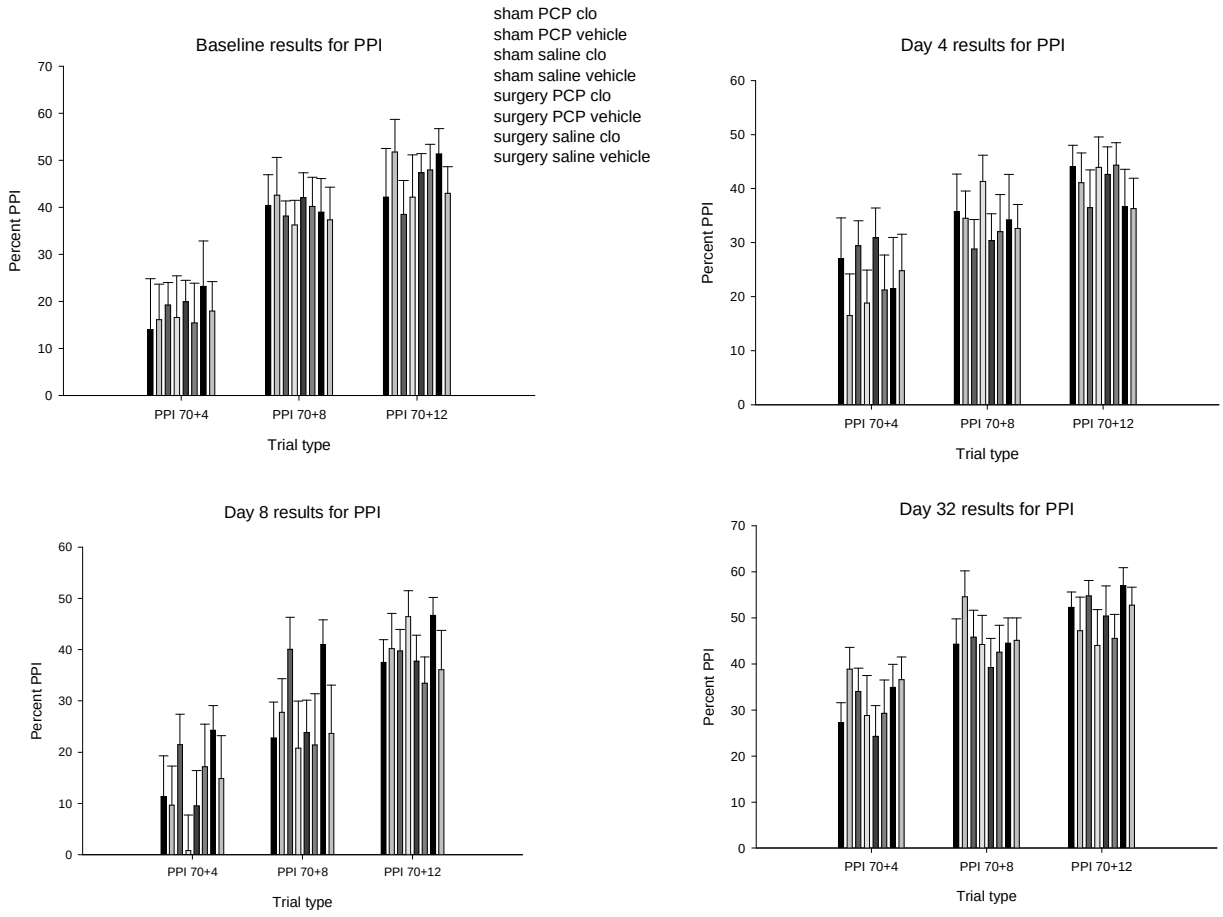

Figure 6 Prepulse inhibition

Mean (+/- SEM) percentage of prepulse inhibition for all animals (n=12). Day 4 testing occurred just prior to the first dose of PCP, and Day 8 testing was conducted 10 minutes following the fifth dose of PCP treatment to investigate acute effects of PCP treatment. The final test of PPI was done just before beginning testing in the place escape avoidance paradigm. To calculate the percent prepulse inhibition, each animal's response was calculated for the three prepulse trials separately according to the following formula: (startle amplitude on PULSE ONLY trials – startle amplitude on prepulse trials) / (startle amplitude on PULSE ONLY trials) * 100. It was expected that Day 8 testing would reveal a significant decrease in the percentage of PPI for animals receiving PCP; however, no significant effects were found. Instead, the analysis revealed no significant effects for surgery, PCP, or clo treatment at any test time.

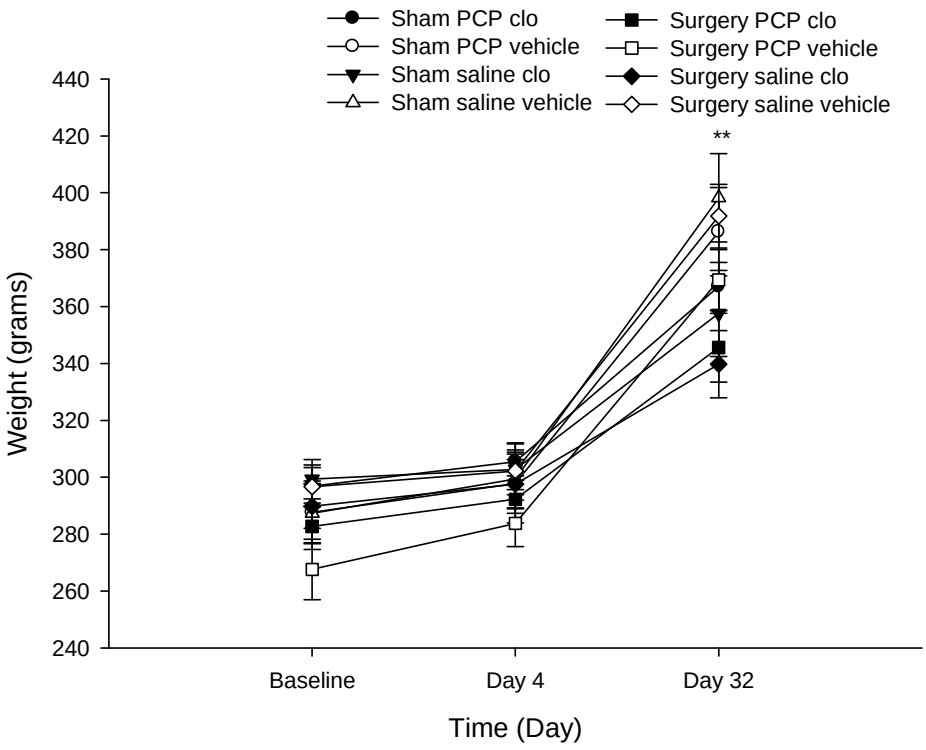

Figure 7 Weight

Mean (+/- SEM) weight for all animals (n=12). Animals were weighed daily just prior to any manipulations. At baseline and Day 4, there were no significant differences between groups. However, clo treated animals displayed significantly less weight gain by the end of the study (Day 32). **=p<.01

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Jessica Boyette-Davis earned her Bachelor of Science degree in Psychology from Tarleton State University, a branch of the Texas A&M University system, in 2001. She returned to school in 2005, and earned a Master of Science degree in Experimental Psychology in 2007. After graduating with a Doctor of Philosophy degree in Health Psychology in 2009, she will begin work at a post doctoral position within the Anesthesiology Department at the University of Texas MD Anderson Cancer Center. Her professional goal is to obtain a tenure track position at a research university.