

Acoustic Startle Response and Prepulse Inhibition: Sex Differences with Cocaine

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Abstract

Schizophrenia is a debilitating neurological illness and in this study, our focus is on an aspect of neuro-cognition that is believed to explain many of the attention and cognitive deficits associated with schizophrenia. The acoustic startle response paradigm is applied to the animal model to test the gain or loss of prepulse inhibition (PPI). A decline in prepulse inhibition has been used as a direct correlate of dysfunctional sensorimotor gating which is measured in this study as an increase in startle amplitude or V_{max} . With the injection (ip) of cocaine we induced psychosis in male and female murine animals. We compared changes in the acoustic startle response after administration of cocaine using physiological saline as a control. Sex response differences were analyzed with two-way ANOVA PRISM software by Graph Pad and significant differences were found between both dosage variation and gender. Empirical research in our laboratory with Neuromolecular Imaging reveals the pharmacokinetics of cocaine induced sex differences involved in the area of the mesocorticolimbic biogenic amine systems. In previous studies of the acoustic startle paradigm in the Broderick lab, higher doses of cocaine were used. In this investigation, low doses of cocaine were administered to compare to higher doses as different dose responses are seen when studying typical versus atypical antipsychotics. Furthermore, subtle changes and variations of responses between sexes at the lower doses may belie the underpinnings of the mechanism of such an atypical medication, risperidone.

Keywords: Acoustic Startle Response; Prepulse Inhibition; Cocaine Psychosis; Mesocorticolimbic System; Nucleus Accumbens; Schizophrenia; BRODERICK PROBE®

Introduction

In this study, we have applied the acoustic startle response (ASR) and prepulse inhibition (PPI) paradigm to cocaine induced psychosis in an animal model as it relates to schizophrenia. Induced cocaine psychosis is well known to parallel the symptoms of schizophrenia and can be used to better understand and treat this debilitating disorder in humans. Attention deficits have been known to be one of the most common symptoms of this pathology. Researchers have been attempting to unravel this psychopathology and its underlying causes which is a great hindrance in information processing. It is a loss of sensorimotor gating in the mesocorticolimbic system where we find one of the neural pathways suitable for behavioral analysis and potential pharmacological treatment of psychosis. It is well known that schizophrenic patients have a unique problem in overcoming the distracting effects that occur when stimuli that require information processing are presented in rapid succession [19]. The Acoustic Startle Response/Prepulse Inhibition paradigm uses this premise to test induced psy-

chosis with analysis of the amplitude of the startle response to a strong sensory stimuli when preceded (30 - 500 ms) by a weak stimulus or prepulse [22]. A reduction in the magnitude of the startle response (V_{max}) is indicative of normal sensorimotor gating. A deficit in PPI is believed to underlie the cognitive impairments of the disease and identical parameters in animals and humans, is supported by the use of dopamine agonists. Subsequent treatment with neuroleptics, gives credence to the ASR/PPI model for heuristic experimentation and future novel therapeutics for humans [25]. Many studies using this paradigm have demonstrated sex differences in PPI in both humans and animals, we continue this research with the administration of varying cocaine dosage (and saline as placebo) between both males and females murine animals. This work is an extension of previous application of the ASR/PPI paradigm by Broderick and Rosenbaum (2013) where ip injection of higher drug dose was used in murine animals. This data showed significant differences with cocaine dosages and following this analysis we decided to repeat the acoustic startle paradigm with lower dosages of cocaine. In this present study, between the male and female murine animals, that were indeed isolated from each other, our gathered data measured the change in startle amplitude or V_{max} as opposed to change in PPI. The observed subtle variations between sexes and cocaine dosages parallel the effects observed and well known in the Broderick lab of the biphasic antipsychotic risperidone [28]. These subtle changes may bring us closer to a better understanding of the neural mechanisms of typical and atypical neuroleptics. The Broderick lab has also observed female murine animals to be more sensitive to stimuli due to hormonal changes especially during phases of the estrus cycle. This cyclic behavior in line with the administration of cocaine appears to bring out the typical and atypical behavioral responses associated with psychosis much more in female animals when considerably isolated from the males in a separate room. Indeed, in the Broderick lab, we are the first to observe and publish cocaine as a cause of asynchrony in endogenous brain rhythms which we believe is the cause of many diseases [5]. This temporal synchrony, which is a complex flow of neuronal firing and neurochemical release along with motor function, needs to be restored to treat such pathologies as psychosis.

Materials and Methods

Animals

All of our experiments were performed on adult male and female Sprague-Dawley murine animals. Animals were purchased from Charles River Laboratories, Kingston, NY. They were housed in a controlled animal facility; males separated from females. The Animal Care Facility operates under the auspices of the CUNY, City College Institutional Animal Care and Use committee (IACUC) in compliance with National Institute of Health (NIH) guidelines. Food (Purina Rat Chow) and water available ad libitum in a home cage. Prior to each experiment the animal was caged in the senior investigator's lab for one night with food and water available as before. Females in Group C were housed in a separate room from the males to test hormonal stress. Each experiment was performed on one animal at a time (one in a 24 hour period) each being administered a specific drug dosage if not physiological saline. Animal weights for both genders ranged from 250g to 490g on day of experiment.

Vaginal smears using exfoliate cytology

Samples were collected before and after injections within a 30 minutes period. Females were swabbed with saline-soaked cotton tip and dotted on a microscope slide. Samples were observed at 40x objective lenses using an Invert Research Microscope (Nikon EclipseTI) Zeiss Axioplan 2 Imaging and Cari Zeiss Vision GmbH. The vaginal smears were stained with a Diff staining kit (IMEB, Inc.) and analyzed according to four stages: proestrus, estrus, metestrus, and diestrus. Samples were assessed based on the proportions of the type of cells to determine the appropriate stages. There were three types of cells: round nucleated epithelial cells, irregular shaped anucleated cornified cells, and little round leukocyte cells. The proestrus phase had prominently epithelial cells. The estrus phase had cornified cells. The metestrus phase had an equal amount of all three cells. Finally, the diestrus phase consisted of predominantly leukocytes.

Electrical resistance

Estrus cycle stages were studied by measuring the electrical resistance of the vaginal mucosa (EC40; Fine Science Tools). Subjects were held in hand on their backs, and a probe was placed in the vaginal opening as a recorder calculated the electrical resistance. This

was performed before and after injection with 2.5 mg/kg cocaine and saline and prior to the vaginal smear swab. Statistical analysis was performed on the difference between pre- and post-electrical resistance for the two treatments. A one way analysis of variance (ANOVA) and post hoc Bonferroni test were performed. Alpha significance was set at $p < 0.005$.

Protocol: Acoustic startle response and prepulse inhibition

The ASR/PPI paradigm consists of 4 blocks of 3 different trials performed on each animal. Trial one is habituation, trial two is injection and trial three is post-injection. Habituation trials were preceded by a 5 minute acclimation period and each injection trial proceeded by acute injection of a specific dose of cocaine or physiological saline (not dose specific). Thus, there are four injections, one for each of the 4 blocks per animal. The cocaine dosages were either 2.5 mg/kg, 5.0 mg/kg or 10.0 mg/kg and injected intraperitoneally with the injected amount dependent upon animal weight at time of testing. Within each of the 3 trials there are 25 auditory stimuli presented to the animal in the acoustic startle chamber. The acoustic startle chamber is an SR-LAB model provided by San Diego Instruments, San Diego, CA. This equipment is automated to record the startle response of small animals. The chamber consists of a cylindrical enclosure on a plexiglass base. There is a speaker mounted 24 cm above the animal which provides the background noise, prepulse stimuli and startle stimuli. All of this is controlled by the SR-LAB software and the startle responses are transduced by a piezoelectric accelerometer mounted below the cylinder and recorded as data on a computer (see SR-LAB Manual). We have taken this data of the acoustic startle response (V_{max}) and concatenated it to be compatible and processed on Excel software by Microsoft. The 25 stimuli in each of the 3 trials (repeated four times) consists of the following 5 types in a pseudorandom order; 1) No stimulus, broadband 75 decibels. 2) Pulse alone of 120 decibels. 3) Prepulse of 95 decibels and a pulse of 120 decibels. 4) Prepulse of 105 decibels and a pulse of 120 decibels. 5) Prepulse of 115 decibels and a pulse of 120 decibels.

Results and Discussion

Sex differences in acoustic startle response after cocaine in group A and group B

The following results comprise Habituation (red line), Injection (blue line) and Post-Injection (green line). Habituation precedes all acute studies to bring the animal to a state of acclimation to the environment in the acoustic startle chamber creating a baseline (V_{max}) response prior to each Injection. The Injection is the display of acoustic startle response (V_{max}) following each ip administration of cocaine. The Post-Injection data represents the acoustic startle response (V_{max}) at a time when the effects of cocaine show indications of most significance.

In figure 1 (Group A) there is a significant sex difference in the acoustic startle response. The transduced motor behavior or average V_{max} increases in males signifying a loss of PPI. We observe this at injection and post-injection of 5.0 mg/kg dosage of cocaine while the opposite is seen in females. The data shows that the males are more sensitive to the acoustic startle stimuli while the females demonstrate an increase in PPI with a decreasing average V_{max} .

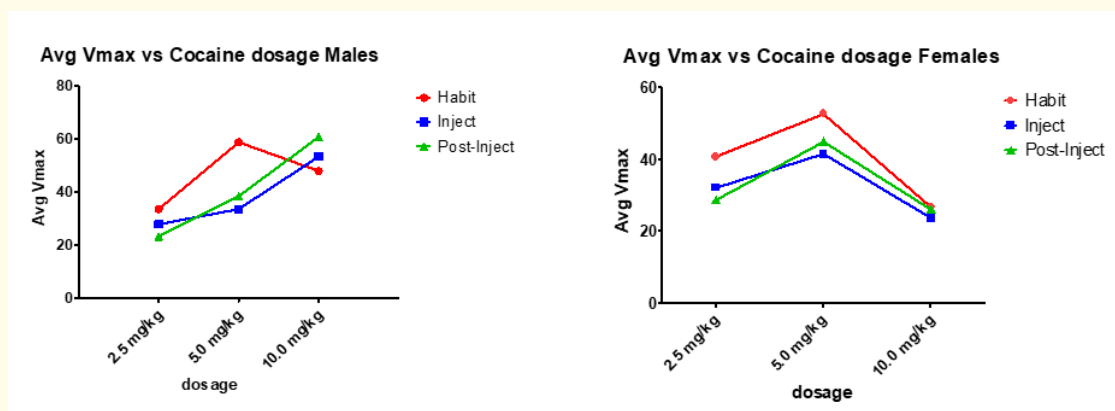


Figure 1: Group A: The data illustrate a loss of PPI in males with an increase in cocaine dosage while the females response is a gain in PPI. This is most apparent following injection and post-inject of 5.0 mg/kg cocaine. Two way ANOVA indicated significance for sex/dosage interaction with $F(2, 12) = 10.06$ and $p = 0.0027$ and for varying dosage alone with $F(2, 12) = 5.53$ and $p = 0.0119$. It should be noted that each average V_{max} for each dosage is based on four acute ip administrations of cocaine in the animal.

In figure 2 (Group B) we have repeated the paradigm with male and female Sprague-Dawley murine animals. Group B shows the same trend in acoustic startle response as seen in Group A. The injection and post-injection data representing the average V_{max} , indicates a loss of PPI in males and a gain in females after ip administration of 5.0 mg/kg dosage of cocaine.

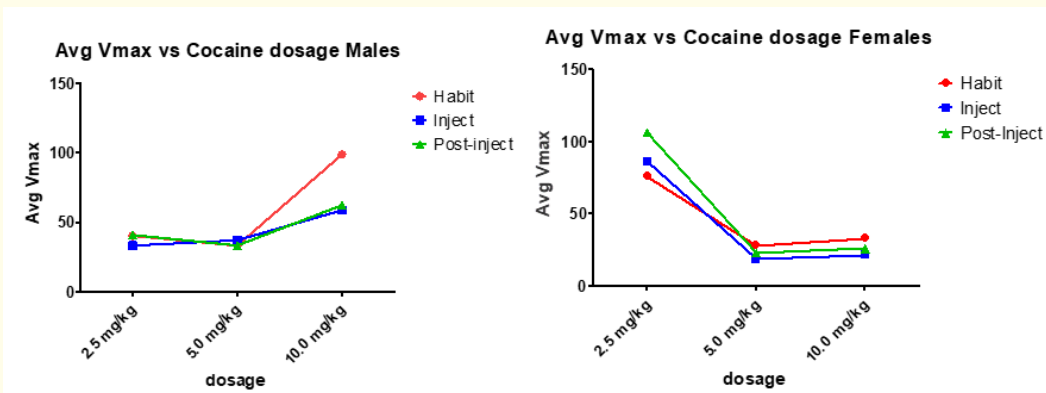


Figure 2: Group B: As in Group A, males showed an increase in overall startle response with increase in cocaine dosage (based on four acute injections of cocaine for each animal per dosage). Females had lower V_{max} averages with an increase in cocaine dosage. Two way ANOVA had repeated significance for gender/dosage interaction as with the previous group with $F(2, 12) = 27.24$ and $p < 0.001$ and for varying dosage alone, $F(2, 12) = 13.75$ and $p = 0.0008$.

Acoustic startle response after cocaine in group C: Isolated females

In figure 3 (Group C), we have tested 6 isolated female murine animals with the ASR/PPI paradigm. This group is different from the previous groups as they were isolated in a separate room from the males. The isolated females injection and post-injection data following the administration of 5.0 mg/kg cocaine indicate a decline in percentage PPI.

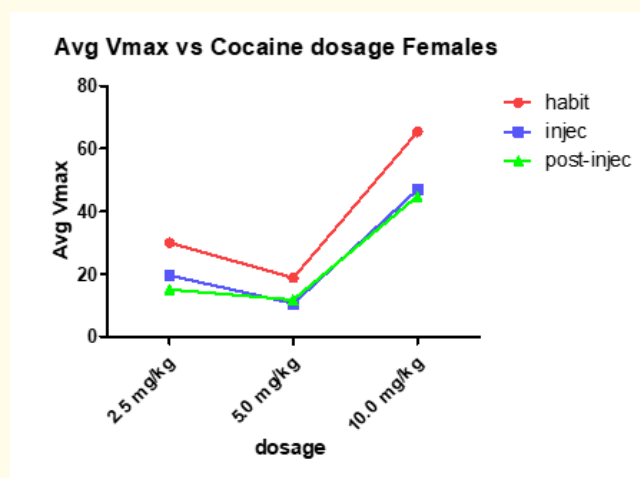


Figure 3: Group C: This group exhibited an increase in V_{max} across cocaine dosage. Thus, there is a loss of PPI in contrast to the first 6 females tested in Groups A and B. ANOVA showed once again varying dosage to be significant; $F(2, 4) = 90.66$ and $p = 0.0005$.

Sex differences after physiological saline

In figure 4a and 4b, our data shows that physiological saline according to weight gives expected results of no significance compared to cocaine.

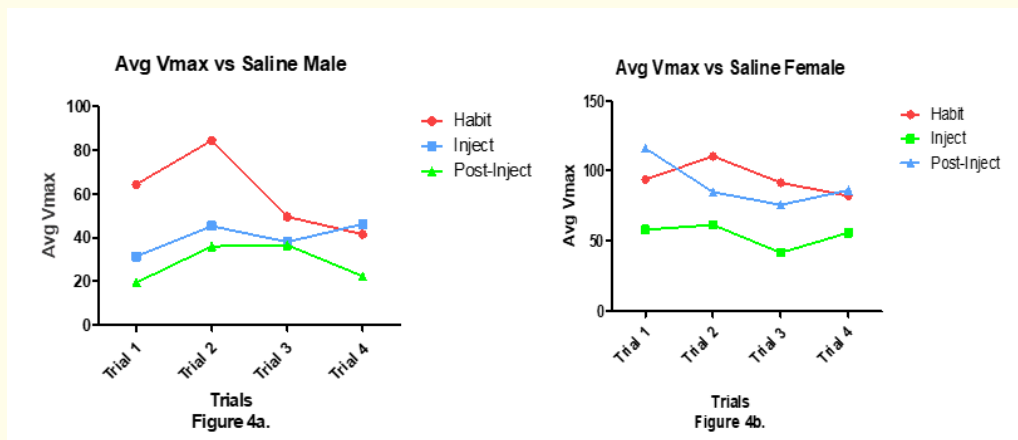


Figure 4a and 4b: Male and female reactions to physiological saline. There is no overall significant effect across the 4 trials.

Why sex differences in the acoustic startle response after cocaine?

With the application of the acoustic startle paradigm and induced cocaine psychosis in the murine animal model, sex differences have been observed in previous studies in this lab [13]. Varying dosages of cocaine were administered (ip) with significant effects on prepulse inhibition (PPI); a measure of sensorimotor gating. Indeed, a decline further descending from the normal PPI is found in schizophrenia as well as other neuropsychological pathologies such as manic depression. Furthermore, the simple sensorimotor gating pathway in the brain allows for novel heuristic paradigms in line with previous studies of neurochemistry. The four synapses in this mesocorticolimbic circuit are the auditory nerve, the posterioventral cochlear nucleus, the ventral nucleus of the lateral lemniscus, the nucleus reticularis pontis caudalis and the spinal motor neuron [32]. In the Broderick lab the commingling and innervation of both dopamine (DA) and serotonin (5-HT) in these neural pathways is well known [3]. In this study we want to bring out the more subtle pharmacokinetic and behavioral responses with attenuated dosages of cocaine. Moreover, we emphasize the changes in the parameter in V_{max} , the amplitude of the startle reflex, as well as the change in PPI as a measure of sensorimotor gating. The significance in our data mimic the effects seen in typical and atypical antipsychotics and their treatment of positive and negative symptoms of schizophrenia. We believe this to be in line with the biphasic effects of the atypical antipsychotic risperidone [28]. Typical antipsychotics affect the positive symptoms of psychosis as dopamine antagonists binding to the D_2 receptor in the nigrostriatal pathway which runs parallel to the mesocorticolimbic pathway, while atypicals act on D_2 and 5-HT₂ receptors in the mesocorticolimbic pathway with success in treating both positive and negative symptoms [28]. Risperidone acts more like an atypical at low dosages and a typical at higher dosages [28].

The data, in Groups A and B, between isolated male and female murine animals show the males to be more sensitive following administration of cocaine with both injection and post-injection startle response. This increase in V_{max} indicates a loss of PPI. The females however, have an injection and post-injection response where overall PPI is maintained particularly at higher dosages of cocaine as some loss in PPI is observed at lower dosages. To further test these responses 6 female murine animals (Group C) were administered cocaine considerably more isolated from the males in a separate room.

In Group C, the females maintained PPI at the low dosages of cocaine as observed in the injection, post-injection data; PPI was lost at the higher dosages. These typical, atypical biphasic injection, post-injection responses may underlie sexual dimorphism in sensorimotor gating. Although the males and females in Groups A and B could be demonstrating hormonal or pheromone effects, the more prominent data from the Group C isolated females may point towards injection, post-injection PPI changes due to the different phases of the estrous cycle. In human studies in healthy young women as well as in animals, it was found that there is a loss of PPI during the luteal phase caused by high levels of estrogen. As with cocaine, estrogen can influence dopaminergic activity in the acoustic startle neuronal pathway particularly the nucleus accumbens and in another study, it was shown that females with a small loss of PPI had a significant increase in levels of progesterone from the follicular to the luteal phase [24]. Indeed, progesterone may play a role in dopamine release by modulation of estrogen at low and high dosages and as a serotonin antagonist at the 5-HT₃ receptors. Moreover, it is also well known to interact with nicotinic cholinergic receptors and it is even suggested that progesterone may act as an endogenous antipsychotic with potential contribution in the treatment of psychosis [24].

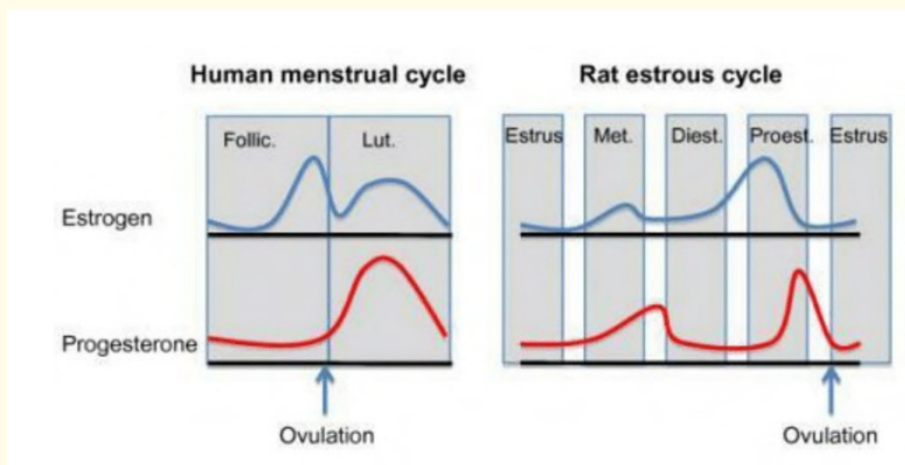


Figure 5: The human menstrual and murine animal estrous cycles [34]. Both Cycles illustrate the change in ovarian hormones estrogen and progesterone, with the human follicular and luteal stages and the murine animal proestrus, estrus, metestrus, and diestrus stages.

In our lab, the effects of ovarian hormones have been extensively studied in the application of exfoliate cytology to examine vaginal smears at all four stages of the estrous cycle following administration of not only cocaine but nicotine as well in the murine animal [14,34]. Taken together, the ASR/PPI paradigm with cocaine and the nicotine study demonstrate the changes induced by these drugs of the murine estrous cycle. The four stages of the murine estrous cycle are: proestrus, estrus, metestrus, and diestrus [34]. Nicotine was administered in four doses (ip) in four different female murine animals with vaginal smear analysis to determine the effects of nicotine on estrogen and progesterone concentrations possibly causing a change in the estrous cycle [34]. The vaginal swab data proved this hypothesis to be valid; pre-drug administration estrous phase; proestrus, metestrus or diestrus, was shifted to the estrus phase with a significant decrease in estrogen and progesterone. It is believed that these ovarian hormones may be protective of nicotine addiction and explain female sensitivity compared to males. Moreover, as nicotine is a nicotinic cholinergic receptor agonist, it can have an effect on periphery muscular reaction to a stimulus thus, potentially affecting prepulse inhibition of the startle response. Indeed, further application of nicotine to the startle response paradigm would be of great interest. In a similar analysis in the Broderick lab, exfoliate cytology of vaginal smears were examined following (ip) injection of cocaine [14]. However, in a novel approach in this same previous study, electrical resistance of the vaginal

mucosa was measured, successfully indicating a direct change in voltage with each phase of the estrous cycle [14]. It was determined that when administering the same dosages of cocaine as presented here, cocaine does in fact change the phases of the estrous cycle in both vaginal exfoliate data and in the novel technique of measuring vaginal electrical resistance [14]. Thus, not only does this novel approach correlate with the observed cytology but offers promise of a technique where less harm is done to the laboratory animal. These studies can help explain sexual dimorphism in drug abuse and addiction and elucidate sex differences in psychosis in the mesocorticolimbic and nigrostriatal neural pathways. This also leaves us asking, how are hormonal changes playing a role, not only in females, but also in the isolated male animals?

Conclusion

This lab has explored the effects of cocaine and novel drugs such as atypicals to better understand and treat schizophrenia [10]. In previous studies in this lab we have applied the ASR/PPI paradigm with cocaine induced psychosis looking at sex differences in the animal model. However, in this follow up study we are administering lower dosages of cocaine to induce psychosis in the male and female murine animal and have found subtle effects are brought out which mimic the varying effects of typical and atypical antipsychotics such as risperidone. Furthermore, we looked at how sex differences may alter or modulate sensory motor gating in a group of isolated female animals (Group C). These female murine animals were housed in a separate room from the males at the CCNY animal facility. In line with this study and previous data from our lab on the estrous cycle and cocaine, we can conclude that cocaine's effect on shifting the estrous cycle can change responses to the acoustic startle response as we observed in females in Group C. This is also supported by the contrast in data in isolated males and females in Groups A and B as we believe hormonal stress following cocaine can bring out the subtle atypical effects which may be associated with the changes in estrogen and progesterone. The overall importance of progesterone as an endogenous atypical in restoring what the Broderick lab calls temporal synchrony requires further exploration with novel approaches to the acoustic startle paradigm and potential treatments of neuropathology. It is most interesting to suggest that these unique studies regarding low dose cocaine may well lead to a novel field of microdosing cocaine and other psychostimulants.

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