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Effects of Chronic Fluoxetine and Paroxetine Treatment on Affective Behavior of Male and Female Adolescent Rats

Zachary R. Harmony

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Author Interview

Which professors (if any) have helped you in your research or creative activity?
Dr. Cynthia Crawford has helped me with my research.

What are your research or creative interests?
My research interests are in animal models of psychiatric orders, neurobiology of depression and behavioral neuroscience.

What are your plans after earning your degree? What is your ultimate career goal?
I plan to earn a M.A. in the General Experimental Psychology program here at CSUSB and continuing researching. My ultimate goal is to earn a Ph.D. in Clinical Neuropsychology and work in an applied setting.

Introduction

Major depressive disorder (MDD) is an affective mood disorder with symptoms characterized by persistent and pervasive sadness, as well as low self-esteem and a loss of interest or pleasure in activities (Maughan, Collishaw, & Stringaris, 2013). Due to the negative symptoms MDD produces, individuals suffering from this disease may encounter a reduction in marital functioning, timing and stability, parental functioning, education, employment status, and financial success (Kessler, 2012). Also, MDD is commonly associated with many chronic physical disorders, such as arthritis, asthma, cancer, cardiovascular disease, diabetes, hypertension, as well as chronic respiratory disorders and pain conditions (Kessler, 2012).

Out of all mental disorders MDD is the fourth leading cause for disability worldwide and is projected to be the second leading cause by 2020 (Kessler, 2012). Depression is a commonly occurring disorder with lifetime prevalence rates ranging from 1.5-19% (Kessler, 2012). Many individuals that seek treatment for MDD often find the ailment to be chronically reoccurring (Kessler, 2012). Within a year there is a one third to one half rate of reoccurrence for depressive episodes in lifetime cases (Kessler, 2012).

The onset of many psychological disorders can appear at any time across ones lifespan (Wittchen, Nelson, & Lachner, 1998). As for MDD, its development can be seen more commonly in childhood and adolescence with a prevalence rate of 4-8% for adolescents and 2% in childhood (Hazell, 2009; Wittchen et al., 1998; Kessler, Avenevoli, & Merikangas, 2001; Nardi, Francesconi, Catena-Dell'osso, & Bellantuono, 2013). Many children and adolescents suffering from depression tend to have a stronger propensity for social withdrawal, substance abuse, and other mental disorders, as well as a decrease in school performance and social skills (Kessler et al., 2001; Nardi, Francesconi, Catena-Dell'osso, & Bellantuono, 2013). Within the pediatric population, there is a 40-90% rate of co-morbidity with other conditions such as, dysthymia, autism spectrum disorders, ADHD, and substance abuse (Vogel, 2012). Another complication that is of major concern is the increased risk of suicide within childhood and adolescent populations due to the effects of major depression (Vogel, 2012).

Within this young and vulnerable population, it is possible that the diagnosis of childhood and adolescent depression may often remain unidentified, as a given depressive episode may not reach the diagnostic threshold for MDD (Nardi, Francesconi, Catena-Dell'osso, & Bellantuono, 2013). The symptoms that linger from an undiagnosed case of MDD can potentially contain chronic clinical and social implications, as well as lead to a fully developed case of MDD for the depressed child (Nardi, Francesconi, Catena-Dell'osso, & Bellantuono, 2013). Clinical features of MDD symptoms in children and adolescents do not correlate directly with the symptoms exhibited by adult populations (Nardi, Francesconi, Catena-Dell'osso, & Bellantuono, 2013). Symptoms in adolescent populations are duly expressed through somatic complaints, including irritability, loss of energy or fatigue, abdominal pain, and headaches (Nardi, Francesconi, Catena-Dell'osso, & Bellantuono, 2013).

In regards to treatment of MDD, there is a wide range of antidepressants that are efficacious for use in adult populations (Ryan, 2005). The first forms of psycho pharmacotherapy for depression were discovered in the 1960's and are characterized as first generation antidepressants, known as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) (Olver, Burrows, & Norman, 2001; Slattery, Hudson, & Nutt, 2004). Due to these compounds broad method of action by nonspecifically increasing monoamine levels in the synapse through reuptake inhibition or reduced metabolism, consequential side effects are expressed (Olver, Burrows, & Norman, 2001). As a result of these adverse side effects patient compliance with MAOIs and TCAs are generally low (Montgomery, 2006). Subsequently, a second generation of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) was developed to improve on method of action and safety (Olver, Burrows, & Norman, 2001).

As for childhood and adolescent populations, the options for treatment of MDD are far less (Gordon & Melvin, 2013; Ryan,

2005). Specifically, in 2003 the FDA issued the SSRI fluoxetine as the only antidepressant that could safely be used within the pediatric population (Gordon et al., 2013; Masi, Liboni, & Brovedani, 2010). Compared to adults, adolescents have different pharmacodynamics and pharmacokinetics (Gordon et al., 2013). Consequently, it appears that there is some evidence for age-dependent effects of SSRIs in humans and rodents (Olivier, Blom, Arentsen, & Homberg, 2011).

Within the US the rate of suicide for adolescents is approximately seven for every 100,000 individuals and most of those whom committed suicide were suffering from a mental disorder and half from MDD (Ryan, 2005). Attempted suicide rates for adolescents suffering from MDD are between 20-24% and rates of suicidal ideation are 15-66%. Given the introduction of psychopharmaceutical interventions for MDD in the form of antidepressants, there appears to be a correlational decrease in rates of suicide for adolescents (Vogel, 2012). Despite this correlation there has been an increase in suicidal ideation and attempts among adolescents who are taking these antidepressants (Vogel, 2012). The risk ratio for suicide attempts and suicidal behavior or ideation as defined by the FDA for fluoxetine is 0-92 and for paroxetine 2-65 (Ryan, 2005). In regards to paroxetine, recommendations for prescribing the drug to depressed pediatric populations has been greatly cautioned due to paroxetine's tendencies to increase the risk of deliberate self-harm or suicidal ideation (Soomro, 2008; Karanges et al., 2011). Fluoxetine on the other hand, has received adequate acceptance for treatment of MDD in the use of pediatric populations (Hazell, 2009; Gordon et al., 2013)

The clinical efficacy of fluoxetine and paroxetines use in childhood and adolescence remains to be certain due to differences observed in associated risk of suicidal ideation or behavior and potential benefits from the SSRIs (Soomro, 2008; Masi et al., 2010; Karanges et al., 2011). Perplexingly, these SSRIs are similar in both composition and method of action that is by blocking the serotonin transporter in the presynapse and thus increasing the amount of serotonin in the presynaptic membrane (Fitzgerald & Bronstein, 2013). Consequently, the aim of the present research study is to further extend the knowledge on the age-dependent effects of chronic fluoxetine and paroxetine treatment in adolescent male and female rats, specifically in regards to anxiety and depression.

Furthermore, we aspire to measure depression through the use of sucrose preference for anhedonia, meaning the inability to draw pleasure from previously joyful experiences. Also, in regards to measuring anxiety we will be using acoustic startle reflex, light/dark box, and elevated plus maze. The aforementioned tests are valid measures of depression due to their manipulations that simulate states of depression through maternal separation, chronic mild stress or chronic dexamethasone treatment, dull sucrose preference, a reduction of time spent in the open arms of elevated plus maze, a reduction of time spent in the lit arena of the light/dark box, and a increase of prepulse inhibition and habituation in the acoustic startle response (Hill, Hellemans, Verma, Gorzalka, & Weinberg, 2012; Leussis, Freund, Brenhouse, Thompson, & Andersen, 2012; Casarotto & Andreatini, 2007; Drapier et al., 2007; Quednow et al., 2006; Tsoory, Cohen, & Richter-Levin, 2007; Yacoubi, Rappeneau, Champion, Malleret, Vaugeois, 2006). Antidepressant treatment subsequently serves as a method to improve scores on these tests (Casarotto & Andreatini, 2007; Huot, Thrivikraman, Meaney, & Plotsky, 2001; Wang, Jiao, & Dulawa, 2011; Quednow et al., 2004). Due to the present lack of definitive evidence in the efficacy on the use of SSRIs in children under the age of 13 (Vogel, 2012), we aim to examine the SSRIs effects in this vulnerable population with rats starting on postnatal day (PD) 30. As a result of the prevalence rates of adolescent MDD being twice as high for female humans than males, we chose to investigate the effects of these SSRIs on both sexes (Vogel, 2012; Frackiewicz, Sarmek, & Cutler, 2000; Scheibe, Preuschhof, Cristi, & Bagby, 2003).

Materials and Methods

Subjects

A total of ___ male and female rats of Sprague-Dawley descent (Charles River Laboratories, Wilmington, MA), born and raised at California

State University, San Bernardino (CSUSB) were used. Litters were culled on PD 3 to a maximum of 10 rat pups. Pups were housed with the dam until PD 20. After weaning, rats were housed in group cages with same-sex litter mates (4-6 rats per cage). After the sucrose preference test (PD 60), rats were single housed for the remainder of the behavioral experiments. A temperature of 22-24°C and a 12-hr light/dark cycle was held inside the colony room. All animals were treated according to the "Guide for the Care and Use of Mammals in Neuroscience and Behavioral Research" (National research Council, 2010) under a research protocol approved by the Institutional Animal Care and Use Committee and CSUSB.

Drugs

Fluoxetine hydrochloride and paroxetine hydrochloride was obtained from Toronto Research Chemicals (Toronto, Canada). Both fluoxetine and paroxetine was dissolved in a 50% dimethyl sulfoxide (DMSO)/water solution and injected intraperitoneally (IP) at a volume of _ ml/kg.

Apparatus

EPM

The EPM was constructed out of black plastic and was stationed 50 cm above floor level (San Diego Instruments, San Diego). The EPM contained four perpendicularly aligned arms, each of which was 50 cm long and 10 cm wide. The two enclosed arms contained 30 cm high walls, while the two open arms were exposed with a .9 cm lip for the prevention of rats falling of the EPM. The EPM was stationed in the center of a quiet, dimly lit room, with a digital video camera located directly above the maze.

Acoustic startle response

The acoustic startle reflex will be measured with the Coulbourn Animal Acoustic Startle System (Coulbourn Instruments, Whitehall, PA), which contains weight sensitive platforms inside individual sound-attenuating chambers. Ventilation fans built into the chambers produced the background noise. Rats were placed in a small, ventilated holding cage, which restricted extensive locomotion.

Light-dark box

The light-dark box contained a 41 x 41 cm base with photobeam receptors (Coulbourn Instruments, Whitehall, PA). The walls of the chambers were 41 cm high. The dark compartment was composed of a dark plastic box covering half of the base. The plastic box also had a small transition door between the light and dark compartments.

Procedures

Sucrose preference

Rats (N=10-11) began sucrose preference training on PD 26 with a two-bottle choice test. On day one of training, rats were individually housed and habituated to drinking water from two bottles. For the next three days (PD 27-30), one of the two bottles contained either a .5 or 2% sucrose solution. On each of the three days, the bottles were weighed and refilled at the same time every morning. To avoid position preferences, the bottles were systematically switched to either the left or right each day. On the last day of sucrose training, (PD 29) rats were group housed with same-sex littermates. On the following day, rats were treated with paroxetine (2.5 or 10 mg/kg), fluoxetine (10 mg/kg), or vehicle once daily from PD 30 to PD 59. Following the last injection, rats were individually housed and given a final sucrose preference test beginning on PD 59 and ending on PD 60. Sucrose preference was defined using the following formula: [(weight of sucrose ingested) / (weight of water ingested + weight of sucrose ingested) x 100]. Assessment of change in sucrose preference due to SSRI treatment was accomplished by calculating difference scores (i.e., the average of the three baseline scores minus the final difference score).

Elevated plus maze

After the cessation of the sucrose preference test on PD 60, rats designated for EPM testing were individually brought to another quite testing room. Each rat was placed in the middle of the EPM with the head facing the open arm. Rats were allowed to roam freely on the EPM for approximately 5-min. Recordings of the rat's activity on the EPM (time spent in the center and open or closed arms) was documented via a video camera and scored afterwards. Data entries for the open or closed arms were documented when

all four paws crossed the thresholds. Data entry for the center of the EPM was documented when two paws crossed the threshold.

Light-dark box

Following the cessation of the sucrose preference test on PD 60, rats designated for light-dark box testing were brought (two at a time) to a quite separate testing room. Each rat was individually placed into the front right corner of the light-dark box and given 10-min to roam freely. Data was recorded for time spent in each of the light and dark compartments, as well as the frequency of transitions into the light compartment, and beam interruptions in the light and dark compartments.

Acoustic startle reflex/prepulse inhibition

After the cessation of the sucrose preference test on PD 60, rats designated for acoustic startle reflex/prepulse inhibition were brought (two at a time) to a quite separate testing room and were placed into a testing chamber for a 5-min acclimation period prior to the delivery of any stimulus. Each session was conducted using a 70 dB white background noise. On the first and last six trails of the session, a startling stimulus (50 dB above the background (or 120 dB), 40 ms) was presented alone. The remaining trails were presented in a pseudorandom order and included 12 trails (middle trails) with the startling stimulus alone (used to calculate % PPI and average startle amplitude), and 12 trails/prepulse stimulus intensity on which a prepulse stimulus (20 ms) preceded the startling stimulus by 100 ms. The prepulse stimuli were 3, 6, 12, 15, or 18 dB above the background. Additionally, there were 8 trails on which no stimulus was presented, but activity within the chamber was monitored. The inter-trail inter will be 20 s. Startle amplitude on the 12 middle trails during which the startle stimulus alone was presented was averaged. These data were used in the analyses of baseline startle amplitude. Percent prepulse inhibition was calculated as [100 x (average startle amplitude on the prepulse trails/average startle amplitude on the middle startle stimulus alone trials)]. Percent habituation will be calculated as [100 x average startle amplitude on the last 6 startle alone trails/average startle amplitude on the first 6 startle alone trails)].

Expected Results

In regards to body weight, we expect that adolescent rats treated with fluoxetine and paroxetine to have less weight gain than rats treated with vehicle (Homberg et al., 2011; Iñiguez, Warren, & Bolaños-Guzmán, 2010; de Jong et al.,). Specifically, we plan to analyze data from body weights obtained during injections with a 3 x 2 x 30 (pretreatment condition x sex x day) repeated measures ANOVA. Measurement of anhedonia will be achieved through the use of sucrose preference test, in which we expect adolescent rats treated with fluoxetine and paroxetine to show less sucrose consumption and preference than rats treated with vehicle (Iñiguez, Warren, & Bolaños-Guzmán, 2010). Furthermore, we plan to analyze data from the sucrose preference test with a 3 x 2 x 2 (pretreatment x sex x sucrose solution) repeated measures ANOVA. For measurement of anxiety-like behaviors we will be using the elevated plus maze (EPM), in which we expect adolescent rats treated with fluoxetine and paroxetine to spend less time in the open arms of the EPM than rats treated with vehicle (Homberg et al., 2011; Vorhees, Morford, Graham, Skelton, & Williams, 2011; Oh, Zupan, Gross, & Toth, 2009; Iñiguez, Warren, & Bolaños-Guzmán, 2010; Drapier et al., 2007; de Jong et al., 2006). Moreover, we plan to analyze data from the EPM with a 3 x 2 (pretreatment x sex) ANOVA. As for acoustic startle response, we expect adolescent rats treated with fluoxetine and paroxetine to exhibit a consistent startle response where rats treated with vehicle would show a decrease in startle response (Homberg et al., 2011; Vorhees; de Jong et al., 2006). In regards to the light/dark box, we expect adolescent rats treated with fluoxetine and paroxetine to stay in the dark compartment for a longer period of time and take longer to emerge into the light compartment when compared to rats treated with vehicle (Arrant, Coburn, Jacobsen, & Kuhn, 2013). Additionally, we plan to analyze data from the light/dark box with a 3 x 2 (pretreatment x sex) ANOVA.

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