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Peer social interaction is facilitated in juvenile rhesus monkeys treated with fluoxetine

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ABSTRACT

Fluoxetine improves social interactions in children with autism, social anxiety and social phobia. It is not known whether this effect is mediated directly or indirectly by correcting the underlying pathology. Genetics may also influence the drug effect. Polymorphisms of the MAOA (monoamine oxidase A) gene interact with fluoxetine to influence metabolic profiles in juvenile monkeys. Juvenile nonhuman primates provide an appropriate model for studying fluoxetine effects and drug*gene interactions in children.

Male rhesus monkeys 1–3 years of age living in permanent social pairs were treated daily with a therapeutic dose of fluoxetine or vehicle (n = 16/group). Both members of each social pair were assigned to the same treatment group. They were observed for social interactions with their familiar cagemate over a 2-year dosing period. Subjects were genotyped for MAOA variable number of tandem repeats (VNTR) polymorphisms categorized for high or low transcription rates (hi-MAOA, low-MAOA).

Fluoxetine-treated animals spent 30% more time in social interaction than vehicle controls. Fluoxetine significantly increased the duration of quiet interactions, the most common type of interaction, and also of immature sexual behavior typical of rhesus in this age group. Specific behaviors affected depended on MAOA genotype of the animal and its social partner. When given fluoxetine, hi-MOAO monkeys had more social invitation and initiation behaviors and low-MAOA subjects with low-MAOA partners had more grooming and an increased frequency of some facial and vocal expressive behaviors.

Fluoxetine may facilitate social interaction in children independent of remediation of psychopathology. Common genetic variants may modify this effect.

1. Introduction

Social functioning is a major endpoint for pharmacotherapy of depression (Bech, 2005; Healy and McMonagle, 1997). The selective serotonin reuptake inhibitor (SSRI) fluoxetine is approved for treatment of depression in children and is also used to treat social anxiety and autism in children (Williams et al., 2013; Kumar et al., 2012; Scharfstein et al., 2011; Stevanovic et al., 2014), but there is no information on whether fluoxetine specifically improves social function during childhood. In adult depressed patients, SSRIs, including fluoxetine, improve social function (Briley and Moret, 2010; Dubini et al., 1997; Sghendo and Mifsud, 2012). In normal adults, SSRIs (citalopram, reboxetine, escitalopram) have been demonstrated to facilitate social interactions although fluoxetine has not been studied in this regard (Tse and Bond, 2002a, 2002b, 2003, 2006; Tse et al., 2014). Similar studies of SSRI promotion of normal social interactions in children or juvenile animals were not identified in the literature. Based on findings with other SSRIs in normal adult humans, fluoxetine would be expected to facilitate social interactions in children.

In this study we measured peer social interactions in healthy young male rhesus monkeys. Ethical considerations preclude experiments in normal children with psychoactive drugs. A unique potential “side effect” of giving psychopharmacological agents to children is irreversible change in the trajectory of brain development that could lead to permanent impairment of brain function (Christian et al., 2015).

Nonhuman primates, particularly macaque monkeys, have become a valuable model for studies of psychoactive agents that

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translate to children (Gill et al., 2012; Mandell et al., 2011; Mattison et al., 2011; Patterson et al., 2010; Paule et al., 1992; Popke et al., 2001; Rodriguez et al., 2010; Shrestha et al., 2014; Soto et al., 2012). Macaque monkeys undergo a long period of brain development between infancy and puberty when higher cortical functions are being established in conjunction with synaptic pruning (Elston et al., 2010a, 2010b; Rakic et al., 1986) and prefrontal cortex specialization and inclusion in brain circuits (Hill et al., 2010). Nonhuman primates are also a valuable model for studying gene*environment interactions (Barr et al., 2003).

In addition to drug effects, drug*genotype interactions were studied. Individuals within the two Treatment groups (fluoxetine, vehicle) were balanced for common variable number of tandem repeats (VNTR) polymorphisms of the serotonin metabolizing enzyme monoamine oxidase A (MAOA, LPR polymorphism). Each social dyad consisted of two partners in the same Treatment group, but with either the same or different MAOA genotypes (high or low transcription polymorphism). Thus MAOA genotype was also balanced within Treatment group, and individual, rather than dyad, was the unit of analysis. This design allowed evaluation of both variables with efficient use of animals. Monoamine oxidase metabolizes monoamine neurotransmitters including serotonin via oxidative deamination. The MAOA isoform has high selectivity for serotonin (Murphy et al., 1979) and is localized primarily in brain (Westlund et al., 1993). VNTR polymorphisms of MAOA occur in both macaques and humans and can be classified as producing greater (high-MAOA) or less (low-MAOA) transcription of the MAOA gene (Newman et al., 2005; Wendland et al., 2006). As an inhibitor of the serotonin reuptake, fluoxetine has potential to interact with the serotonin metabolism pathway. Interestingly, fluoxetine can also directly inhibit MAOA activity (Mukherjee and Yang, 1999). In metabolomics studies of juvenile rhesus we found that fluoxetine administration interacted with MAOA polymorphism genotype in influencing metabolites in plasma and cerebrospinal fluid (He et al., 2014) indicating a biological basis for an interaction between fluoxetine and MAOA.

MAOA polymorphisms influence risk for, symptom patterns of, and severity of childhood behavior disorders including autism and ADHD (Davis et al., 2008; Cohen et al., 2003; Jaiswal et al., 2015; Verma et al., 2014; Tassone et al., 2011; McCracken et al., 2014; Cohen et al., 2011; Yoo et al., 2009). There is minimal research on MAOA polymorphism effects on behavior of normal infants and children (Zhang et al., 2014, 2011). We previously found that infant and juvenile monkeys with low-MAOA polymorphisms used more expressive vocalizations and facial expressions in social challenge situations (Golub et al., 2012). Hi-MAOA immature monkeys initiated more grooming episodes and displacements than their low-MAOA peers in round-robin testing (Golub et al., 2012) and also solved more cognitive puzzles (Golub and Hogrefe, 2014a). MAOA polymorphisms also interacted with developmental iron deficiency in macaques to influence social behavior (Golub et al., 2012). Based on this background, we hypothesized that MAOA polymorphism genotype would be a modifier of the behavioral response to fluoxetine.

2. Materials and methods

2.1. Assurance of compliance with animal codes

All animal procedures followed the Guide for the Care and Use of Laboratory Animals of the National Research Council and were approved by the UC Davis Institutional Animal Care and Use Committee.

2.2. Animal selection

Thirty-two male rhesus monkey infants were selected from the outdoor group-caged colony at the California National Primate Research Center (CNPRC) at 10 months of age and adapted to long-term indoor pair-housing as described previously (He et al., 2014). Males were selected for study because of the feasibility of obtaining MAOA genotype groups with high and low-expressing genotypes of the X-linked MAOA gene. The population of females homozygous for high and low-expressing alleles available for the study was limited due to the predominance of mixed allele heterozygotes.

2.3. Drug treatment

Drug treatment began at one year of age (367 ± 0.4 days of age, mean ± sem). Half of the group was administered an oral dose of fluoxetine (Webster Veterinary Supply, Devens, MA). Monkeys were trained to receive the daily dose diluted in a flavorful vehicle by oral syringe between 1 and 2 pm. Vehicle controls received only the flavorful vehicle. A dose of 2.0 mg/kg was known to be therapeutic in adult rhesus (Clarke et al., 1999, 1998; Fontenot et al., 2009; Fontenot et al., 2005; Sawyer and Howell, 2011) and determined to be in the therapeutic range for juvenile rhesus (Golub and Hogrefe, 2014b). During the two years of treatment (from 1 to 3 years of age) the dose was initiated at 1.6 mg/kg for the first 11 months and increased to 2.4 mg/kg for the remainder of the study. In a pilot study, serum levels of fluoxetine and its active metabolite norfluoxetine averaged 336 ± 40 ng/mL (mean ± sem) 2–10 h after a single dose of 2.0 mg/kg in rhesus juveniles (Golub and Hogrefe, 2014b). Fluoxetine and norfluoxetine averaged 273 ± 31 ng/mL when measured 20 h after dosing with 2.4 mg/kg in the current study. Comparable values in children are 363 ng/mL measured 8–12 h after dosing in a pharmacokinetic study of pediatric patients treated with fluoxetine at therapeutic doses (Wilens et al., 2002) and 213 ng/mL from a therapeutic monitoring study in pediatric patients (Koelch et al., 2012).

2.4. Study design

The design of the study is shown in Table 1. Most rhesus infants at CNPRC are genotyped for common VNTR polymorphisms of the serotonin transporter gene (SERT, 5HTTLPR polymorphism, LL, SL and SS variant groups) and the serotonin metabolizing enzyme monoamine oxidase A (MAOA, hi-MAOA and low-MAOA variant groups) allowing us to select subjects to balance these variables within treatment groups. SERT polymorphisms were not found to influence social behavior. An extensive battery of behavioral evaluations was conducted (Table S1), including 3, 30-min sessions of social interaction observation conducted 6 months, 12 months and 20 months after initiation of dosing (18, 24 and 32 months of age).

Social observations were conducted in the home housing situation. All animals in the study were housed in an indoor caging room in a suite of two cages (each 60 by 65 by 79 cm) connected by a door. The two cagemates assigned for compatibility by animal management staff remained together throughout the study with the door between the two cages open except during dosing and behavioral testing. Both cagemates were assigned to the same treatment (fluoxetine or vehicle). The sessions were conducted in the afternoon (1500 h) by the same observer seated with a laptop computer in a neutral location that differed for each dyad. Observations using a social ethogram (Table S2) were recorded with Observer software (Noldus Observer XT 11.0, Noldus Information Technology, Netherlands) after a 3 min adaptation period. No more than two dyads were observed on one afternoon.

The ethogram contained 30 social interactions and social