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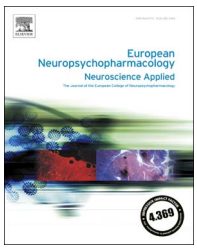

Regulation of emotional response in juvenile monkeys treated with fluoxetine: MAOA interactions

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Abstract
Juvenile male rhesus macaques received therapeutic doses of fluoxetine daily from one to three years of age and were compared to vehicle-treated controls ($N=16$/group). Genotyping for monoamine oxidase A (MAOA) polymorphisms was used to form subgroups ($N=8$) with high and low expression of the gene. Behavioral responses were scored during 30-second exposures to pictures differing in affective content. As expected from its therapeutic effect, fluoxetine decreased the behavioral response to emotionally evocative pictures. A 44% reduction in number of expressive behaviors was seen, but only in subjects with low expression MAOA polymorphisms. In general, this effect occurred for pictures of varying affective content and was not due to altered occurrence of one specific behavior or type of behavior. The drug*genotype interaction was seen after one and two years of treatment and did not reverse one year after discontinuation of dosing. Two potential translational implications are suggested: (1) MAOA genetic polymorphisms may be the source of some of the variability in response to fluoxetine treatment in children; (2) extended fluoxetine treatment during juvenile brain development may result in persistent effects on emotional regulation.

1. Introduction

Fluoxetine was approved in the US in 2003 and in the EU in 2006 for treatment of children with MDD (major depressive disorder), and it continues to be the first line pharmacological treatment for this disorder (Pfalzgraf et al., 2012; Birmaher et al., 2007). The use of fluoxetine in treating depression in children is consistent with its interaction with brain circuits regulating emotional response. In adults and adolescents, regulation of emotional response, as reflected in activation of amygdala and associated brain areas (Delaveau et al., 2011), is shown to be elevated in depression and normalized by treatment with antidepressants

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(Fu et al., 2013) including fluoxetine (Rizvi et al., 2013; Tao et al., 2012). Antidepressants including fluoxetine also affect emotional brain activation in normal adults (Norbury et al., 2009; Pringle and Harmer, 2015). There is some information on the brain activation response to emotional stimuli in depressed children (Gaffrey et al., 2013), but no studies of antidepressant effects. In addition to its use in depression, fluoxetine therapy is approved for use in OCD, but it is also used "off-label" in a variety of other childhood disorders such as anxiety (Birmaher et al., 2003; Strawn et al., 2015), autism (Williams et al., 2013), obesity (Rezvanian et al., 2010), social phobia (Davidson et al., 2004), and Down's syndrome (Costa and Scott-McKean, 2013).

While the efficacy of fluoxetine therapy for depression in children is supported by published studies (Hetrick et al., 2007), many safety issues arise when considering psychoactive drug use in children. The demonstration of increased risk of suicidal ideation in adolescents treated with antidepressants raised the question of whether side effects in children can be anticipated from experience with adults or whether unique unwanted effects can occur. Another issue, more difficult to study in children, is whether developmental treatment can alter the trajectory of brain development with unfavorable long-term consequences. We have addressed these issues in juvenile nonhuman primate model for childhood treatment with fluoxetine at therapeutic doses. The ages of the rhesus macaque subjects in the present study (one to four years of age) correspond roughly to four to twelve year-old children. Previous reports from this project have described dose selection (Golub and Hogrefe, 2014), metabolomic biomarkers of drug action (He et al., 2014), bone growth (Golub et al., 2015), sleep disturbance (Golub and Hogrefe, 2016), and social interaction (Golub et al., 2016).

Macaque monkeys have long been studied as models for emotional response during infant development (Kalin and Shelton, 2003) and are becoming widely employed as suitable animal models for studying psychoactive drugs during juvenile and adolescent brain development (Soto et al., 2012; Shrestha et al., 2014; Rodriguez et al., 2010; Popke et al., 2001; Paule et al., 1992; Patterson et al., 2010; Mattison et al., 2011; Mandell et al., 2011; Gill et al., 2012). The extended period of postnatal brain development, the specialization of higher cortical areas and top-down regulation of lower centers are all common characteristics of primate species' brains. Parallel technical evaluations of brain function can be used in human and nonhuman primates, particularly the noninvasive imaging techniques and structured behavioral evaluations. Single offspring pregnancies, complex social structures, and extensive use of visual information are other valuable parallels to humans that improve translation of this animal model.

The data reported here are from a test paradigm using response to emotionally evocative pictures. This technique is becoming widely used with fMRI to study the brain circuits mediating emotional response and modification of their activation in humans (Delaveau et al., 2011) including children (Perlman et al., 2014). In the current study, response to pictures differing in affective content was recorded as the frequency of occurrence of vocalizations, facial expressions and simple actions used as expressive behaviors in young monkeys. It was hypothesized that fluoxetine would affect regulation of the frequency of these expressive behaviors in comparison with vehicle-treated controls.

Genetic polymorphisms are another factor known to modify brain regulation of emotional response in humans. The influence of genetic polymorphisms can also be studied in nonhuman primates due to sharing of genetic variants among evolutionarily related species. Our study design included subgroups with high- and low-transcription VNTR polymorphisms of the monoamine oxidase A (MAOA) gene. These polymorphisms have been associated with risk for impulsivity, violence/criminality and psychopathology in adolescents and adults, particularly in interaction with early experiences (Byrd and Manuck, 2014; Enoch et al., 2010; Kim-Cohen et al., 2006). They have also been shown to influence brain circuits regulating emotional response (Meyer-Lindenberg et al., 2006). Rhesus monkeys have uVNTR polymorphisms homologous to those seen in humans and behavioral differences have been reported between high- and low-expression genotypes in interaction with environmental variables in monkeys (Newman et al., 2005; Karere et al., 2009). Using emotionally evocative pictures, we have previously shown interactions between developmental iron deficiency and MAOA polymorphisms in our nonhuman primate model of juvenile behavior (Golub et al., 2012).

The present study included low- and high-expression MAOA polymorphisms as an independent variable in the design. The potential for interaction between fluoxetine and MAOA polymorphisms in adults has been demonstrated by the finding that both MAOA inhibitors and SSRIs are effective therapies for depression in adults (Thase, 2012), that MAOA polymorphism genotype is associated with therapeutic response to fluoxetine (Yu et al., 2005), and that both fluoxetine and MAOA polymorphisms can influence the brain circuits mediating response to emotion-evoking stimuli (Tao et al., 2012; Dannlowski et al., 2009). There are few studies of the MAOA polymorphism influences on the behavior of infants and children (Pickles et al., 2013; Zhang et al., 2011; Zhang et al., 2014) and no studies of interactions with psychoactive drugs. The study reported here assessed interactions both during dosing and after discontinuation of dosing.

2. Experimental procedures

2.1. Assurance of compliance with animal codes

All animal procedures followed the Guide for the Care and Use of Laboratory Animals of the US National Research Council (National Research Council, 2011). Protocols were reviewed and approved by the UC Davis Institutional Animal Care and Use Committee prior to implementation.

2.2. Subjects

Thirty-two male rhesus macaques (*Macaca mulatta*) were selected at ten months of age from the outdoor colony of the California National Primate Research Center (CNPRC) and relocated indoors in pair housing with a compatible peer. Selection criteria have been previously described (Golub and Hogrefe, 2016) and allowed for

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