Serotonergic Functioning in Children with Oppositional Defiant Disorder: A Sumatriptan Challenge Study

Heddeke Snoek, Stephanie H.M. van Goozen, Walter Matthys, Hein O. Sigling, Hans P.F. Koppeschaar, Herman G.M. Westenberg, and Herman van Engeland

Background: Several studies support the notion that disturbances in the central serotonergic function are related to impulsive aggression. There is recent evidence from studies on 5-HT1B knock-out mice that this specific receptor is involved in impulsive aggressive behavior. The aim of the present study was to investigate 5-HT1B/1D receptor functioning in normal intelligent hospitalized children with oppositional defiant disorder (ODD).

Methods: The growth hormone (GH) response to a challenge with the 5-HT1B/1D agonist sumatriptan was examined in 20 children with an ODD, of whom 13 had an attention-deficit/hyperactivity disorder comorbidity, and 15 normal control subjects (NC). Blood samples for growth hormone were collected repeatedly between 8:30 and 12:00 AM. Sumatriptan was administered at 10 AM. The effect of stress due to this procedure was assessed by measuring salivary cortisol.

Results: The GH response was significantly stronger in the children with ODD. After sumatriptan injection NC children showed a significant increase in cortisol; no such pattern was present in the ODD group.

Conclusions: The results suggest that the postsynaptic 5-HT1B/1D receptor is functionally more sensitive in children with ODD. Biol Psychiatry 2002;51:319–325 © 2002 Society of Biological Psychiatry

Key Words: Serotonin, aggression, sumatriptan, child psychiatry, 5-HT1B/1D receptors

Introduction

Conduct disorders constitute the most prevalent psychiatric disorder in childhood and adolescence, both in the general population and in clinical samples (Offord et al 1991). Children with an oppositional defiant disorder (ODD) or with a conduct disorder (CD) are at high risk for criminality and antisocial personality disorders in adulthood (Loeber and Stouthamer-Loeber 1998; Rutter and Giller 1983). Several studies support the notion that disturbances in the central serotonergic function are related to aggression and impulsivity (Coccaro and Kavoussi 1996). Experimental animal research and research in adult psychiatric patients converge to suggest that a decrease in the central serotonergic function, reflected by diminished concentration of 5-hydroxyindoleacetic acid (5-HIAA) in the lumbar cerebrospinal fluid (CSF), relates to an augmented aggression score (Higley et al 1992; Tuinier et al 1995). Apart from the invasive CSF method, neuroendocrine challenge studies offer good possibilities to investigate the relationship between central serotonin (5-HT) function and (impulsive) aggression (Coccaro and Kavoussi 1994). Most challenge studies have been conducted using prolactin (PRL) responses to fenfluramine as an index of 5-HT function in the brain. In aggressive adults the picture is more or less clear-cut: the PRL response to fenfluramine has been found to be reduced and inversely correlated with aggression, motor impulsivity, and irritability (Coccaro et al 1989). An elevated PRL response in aggressive adults has also been found (Fishbein et al 1989); however, the subjects in this study were severe multiple drug abusers whereas other challenge studies used adult patients with a personality disorder.

In children the results of studies using various measures of 5-HT are mixed. Because lumbar CSF punctures in children are difficult to execute for medical ethical reasons, most studies have focused on peripheral indices of central 5-HT function, such as whole-blood 5-HT levels or platelet imipramine binding (Stoff and Vitiello 1996). In two previous studies comparing ODD/CD children with normal control subjects, we found that plasma 5-HIAA was significantly lower in the ODD/CD children than control subjects and strongly inversely correlated with aggressive behavior (Van Goozen et al 1999). In one study, Kruesi et al (1990) found lower CSF 5-HIAA levels in disruptive children as compared to children suffering from obsessive-compulsive disorder. By contrast, Castel-
lanos et al (1994) reported a positive correlation between CSF 5-HIAA levels and measures of aggression and impulsivity in prepubertal boys with attention-deficit/hyperactivity disorder (ADHD).

Until now, four challenge studies (all using fenfluramine) have been conducted in children with disruptive disorders. In none of these studies was an inverse relationship between PRL and aggression found. Stoff et al (1992) found no relationship between the PRL responses and aggressivity in pre- and postpubertal boys with disruptive behavior. Halperin et al (1994, 1997) found a significantly enhanced PRL response in young (<9.1 years) aggressive boys with ADHD, whereas the older (>9.1 years) aggressive ADHD boys did not show an elevated response. Finally, Pine et al (1997) reported a positive relationship between the PRL response and aggressive behavior in younger brothers of convicted delinquents. Unfortunately, the Halperin studies (Halperin et al 1994, 1997) as well as the study by Pine et al (1997) did not have a normal control group for comparison, nor did these studies contain a purely aggressive group, because their core group consisted of children with ADHD. Therefore, it is difficult not only to determine whether the PRL response to fenfluramine differs between aggressive and nonaggressive children, but also between different subgroups of children with disruptive behavior.

Fenfluramine is no longer available as a challenge agent because of its adverse side effects. Moreover, it is a nonselective and indirect acting 5-HT receptor agonist, making it impossible to distinguish between the various 5-HT receptor subtypes. Recent studies in mutant mice lacking the 5-HT1B receptors suggest that this receptor might be implicated in impulsive aggressive behavior in rodents (Lucas and Hen 1995). The 5-HT1B knock-out mice appear to be more aggressive toward intruders than their conspecific wild types. This finding fits with the observation that some 5-HT1B receptor agonists have anti-aggressive properties (Olivier et al 1995) and the findings that a reduced brain 5-HT neurotransmission is associated with high levels of impulsivity and aggression. In contrast with these findings, drugs with 5-HT1B receptor antagonistic properties (e.g., pindolol) are clinically not considered aggression-enhancing compounds; however, although the functional effects of 5-HT1B receptors are comparable across species, its pharmacology is not (Barnes and Sharp 1999).

In comparison with fenfluramine, sumatriptan (Imigran, Glaxo Wellcome, Zeist, The Netherlands) is a direct-acting and a more specific 5-HT receptor agonist, in that it has high affinity for the human 5-HT1B and 5-HT1D receptors (Peroutka and McCarthy 1989). Sumatriptan, a well-known antimigraine drug, has been shown to stimulate growth hormone (GH) secretion in normal control subjects without affecting the release of PRL, cortisol (CORT), or adrenocorticotropic hormone (Franceschini et al 1994) suggesting that the release of this hormone following a challenge with sumatriptan can be used as a probe for the 5-HT receptor sensitivity. So far, no studies with sumatriptan in aggressive or antisocial children and adults have been published.

The aim of the present study was to investigate the possible role of the 5-HT1B receptor in the modulation of impulsive/aggressive behavior of hospitalized children with an early-onset ODD. We expect to find a difference in the GH response to sumatriptan administration in these patients as compared to normal control subjects. Because GH levels are also influenced by stress (Delitala et al 1987), we also measured CORT levels to assess possible effect of stress.

Methods and Materials

Subjects

Subjects, all Caucasian (n = 35), were aged between 7 and 12 years [mean age normal control (NC) group = 10.7 (± 1.1) years; mean ODD group = 10.1 (± 1.2) years; F(1,34) = 2.41, p = .13]. The NC children, 9 girls and 6 boys, were recruited from grades 4 to 8 of a regular elementary school (n = 15). None of the NC children showed any disruptive behavior as assessed by the Diagnostic Interview Schedule for Children version 2.3 (DISC-P; Shaffer et al 1996). The ODD group (n = 20) consisted of 16 boys and 4 girls who had met the criteria for ODD (n = 17) or CD (n = 3) as set out in the DSM-IV (American Psychiatric Association 1994). It was considered permissible to include children with a CD in the ODD group, because the overlap in symptomatology and prognosis between the childhood-onset type of ODD and CD is large (96%) (Hinshaw et al 1993; Lahey et al 1992). The ODD group was solicited from an inpatient clinic from the Department of Child and Adolescent Psychiatry, University Medical Center, Utrecht, The Netherlands, specialized in treatment of children with ODD. After extensive diagnostic assessment (psychiatric interviews, psychological assessment of the child, and interviews with the parents, including discussion of the developmental history and observations by child care workers), children were included in the experimental group; consensus on the diagnosis was reached between three psychiatrists (WM, HOS and HvE). Parents of all included children were also administered the DISC-P. The children with ODD had the following comorbid diagnoses: ADHD (n = 13), dysthyemic disorder (n = 4), any anxiety disorder (n = 3), enuresis (n = 3), and encopresis (n = 2). Ten of the ODD children with ADHD comorbidity were being treated with methylphenidate (MPH). All NC children were free of medication. Developmental status of puberty was assessed by examining hormonal levels of plasma insulin-like growth factor 1 (IGF-1) and plasma insulin-like growth factor binding protein 3 (IGFBP-3).

To describe subjects from a dimensional point of view, the Child Behavioral Checklist (CBCL) (Achenbach 1991a) was
completed by the parents of all subjects. All children with ODD scored within the clinical range of the total externalizing scale (sum of the delinquent and aggression scales) on this questionnaire. The children’s teachers completed the teacher version (TRF) of the CBCL (Achenbach 1991b). In order to match the groups on IQ, the NC children completed two subtests of the Wechsler Intelligence Scale for Children-Revised (WISC-R; Wechsler 1974), namely Vocabulary and Block Design. These subtests have a correlation of .90 with the full-scale intelligence quotient (IQ) (Sattler 1992). Full IQ data of all children with ODD were collected as part of the screening procedure at intake. Exclusion criteria included any physical illness, any psychoactive drug with the exception of MPH, a full-scale IQ below 75, overweight (≥97th percentile), or electrocardiogram abnormalities.

The study was approved by the Medical Ethical Committee of University Medical Center Utrecht. Written informed consent was obtained from the parent and verbal assent was obtained from the child after the procedures had been fully explained.

**Sumatriptan Challenge**

Subjects remained on a low monoamine diet for 3 days prior to the challenge procedure. The protocol began after an overnight fast, at 8:15 AM, with the insertion of an indwelling intravenous catheter in an antecubital vein. The catheter was kept patent with 0.5 mL heparin (12.5 units in 5 mL) following each blood sample drawing. Subjects remained awake and semi-recumbent in bed. When subjects were hungry or thirsty they were allowed to eat a cracker and to drink water or apple juice.

Samples for plasma GH were obtained at 8:30 AM and again at 9:30 AM. At 10:00 AM 4 mg sumatriptan succinate (SUM) was administered subcutaneously (s.c.) in the upper arm. Four post-challenge samples of plasma GH and SUM were obtained every half hour until 12:00 AM (see Table 1). Samples were collected in plastic tubes containing ethylenediaminetetraacetic acid and placed immediately on ice until centrifugation, which took place within 2 hours. After separation, plasma samples for GH and SUM analyses were kept frozen at −30°C until assayed. Growth hormone was measured using an immunometric technique on an IMMULITE Analyzer (Diagnostic Products Corporation, Los Angeles, CA). The lower limit of detection was .5 nmol/L and interassay variation was 11.0%, 8.2%, and 7.6% at 2.52 mg/L, respectively (n = 20).

**Psychological Measures**

To assess how children experience different fearful situations, medical interventions in particular, the children completed the Fear Survey Schedule for Children-Revised (FSSC-R; Ollendick 1983; score range: 80–240), which contains a “medical fear” subscale. Also, upon arrival and after the challenge test the subjects were administered the state scale of the State Trait Anxiety Inventory for Children (STAI-C; Spielberger et al 1983; score range: 80–240), which contains a subscale of 12 mood dimensions.

**Statistical Analysis**

Within the pharmacochallenge literature, different response parameters are used. We assessed the GH response to sumatriptan by using two different statistical methods: 1) peak GH (GH3) with baseline levels of GH, gender, age, and hormonal indicators of pubertal development (IGF-1 and IGFBP-3) used as covariates; and 2) repeated measures analyses of variance (ANOVA) with “group” (ODD vs. NC) as between-subjects factor and “time” as within-subjects factor. Repeated measures ANOVAs

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**Table 1. Sumatriptan Challenge Procedure**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Blood sampling</th>
<th>Saliva</th>
<th>Psychological measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:15 AM</td>
<td>Insertion catheter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>08:30 AM</td>
<td>GH1</td>
<td>COR1</td>
<td>VAS 1</td>
<td>STAI-C 1</td>
</tr>
<tr>
<td>09:30 AM</td>
<td>Baseline</td>
<td>GH2 SUM 1</td>
<td>COR2</td>
<td>VAS 2</td>
</tr>
<tr>
<td>10:00 AM</td>
<td>SUM injection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:30 AM</td>
<td>GH3 SUM 2 CORT3 VAS 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11:00 AM</td>
<td>GH4 SUM 3 CORT4 VAS 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11:30 AM</td>
<td>GH5 SUM 4 CORT5 VAS 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:00 AM</td>
<td>GH6 SUM 5 CORT6 VAS 6</td>
<td></td>
<td></td>
<td>STAI-C 2</td>
</tr>
</tbody>
</table>

GH, growth hormone; SUM, sumatriptan succinate; CORT, cortisol; VAS, visual analogue scale; STAI-C, State Trait Anxiety Inventory for Children.
There was a significant main effect of “time” \[F(1.5,43.2) = 298.4, p < .001\], but no effects of “group” or “group by time” interactions. The ODD and NC groups also did not differ at SUM2, the time of the peak response (see Figure 1).

Serotonin in Children with ODD

Table 2. Child Behavior Checklist (CBCL), Teacher Report Form (TRF), and Intelligence Quotient (IQ) by WISC-R in Oppositional Defiant Disorder (ODD) and Normal Control (NC) Children

<table>
<thead>
<tr>
<th>Measure</th>
<th>Children with ODD (n = 20)</th>
<th>NC children (n = 15)</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBCL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention problems</td>
<td>73.0a</td>
<td>8.9</td>
<td>51.9</td>
</tr>
<tr>
<td>Delinquent behavior</td>
<td>72.8a</td>
<td>7.4</td>
<td>52.0</td>
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<tr>
<td>Aggressive behavior</td>
<td>81.1a</td>
<td>10.2</td>
<td>51.1</td>
</tr>
<tr>
<td>Externalizing behavior</td>
<td>77.9a</td>
<td>6.3</td>
<td>45.7</td>
</tr>
<tr>
<td>TRF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention problems</td>
<td>61.8</td>
<td>6.7</td>
<td>51.3</td>
</tr>
<tr>
<td>Delinquent behavior</td>
<td>66.5</td>
<td>7.0</td>
<td>52.3</td>
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<tr>
<td>Aggressive behavior</td>
<td>68.2b</td>
<td>10.1</td>
<td>52.7</td>
</tr>
<tr>
<td>Externalizing behavior</td>
<td>67.3a</td>
<td>9.0</td>
<td>47.2</td>
</tr>
<tr>
<td>IQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total IQ</td>
<td>99.2</td>
<td>15.5</td>
<td>100.0</td>
</tr>
</tbody>
</table>

WISC-R, Wechsler Intelligence Scale for Children-Revised.

*Significant difference between groups (df = 1.34, p < .001).

Mean score of the group is in borderline range.

Mean score of the group is in clinical range.

Single isolated missing values or single isolated outlier values, with an outlier value being defined as an individual value more than 2.5 SDs above the mean value of the group, were replaced by the group averages. Values are expressed as mean (± SD).

Results

Clinical Characteristics and IQ

Relevant IQ, CBCL, and TRF means and SDs are given in Table 2. Clearly, the ODD group scored significantly higher on all subscales of the CBCL and TRF. Their mean CBCL attention problems, delinquent, aggressive, and externalizing behavior scores were in the clinical range, whereas their mean TRF aggressive and externalizing scores were in the borderline range. There were no differences in intelligence (WISC-R).

Sumatriptan Succinate

No differences between the two groups were found in IGF-1 [NC = 223.6 ng/mL (± 78.8); ODD = 188.9 ng/mL (± 67.9), F(1,34) = 2.0, p = .17], and IGFBP-3 [NC = 2.5 mg/L (± .4); ODD = 2.3 mg/L (± .5), F(1,34) = .9, p = .34].

Pubertal Development

One NC subject was excluded from the analyses of GH data because three of the six samples had outlier values. Three subjects (one NC, two ODD) had one outlier GH value of the six samples collected in each individual. These values were replaced by their subgroup averages for the particular sample. No group differences were found in GH levels at entrance [GH1NC = 6.6 mIU/L (± 5.6), GH1ODD = 7.4 mIU/L (± 7.1); F(1,33) = .1, p = .72], nor after an hour’s rest [GH2NC = 1.5 mIU/L (± 1.3), GH2ODD = 2.1 mIU/L (± 2.2); F(1,33) = .9, p = .34]. In both groups, however, there was a significant decrease in GH between GH1 and GH2 [F(1,32) = 22.6, p < .001; see Figure 2].

When analyzing GH2 to GH6, an effect of “group” [F(1,32) = 5.1, p = .03], a main effect of “time” [F(1,8,58.0) = 68.5, p < .001] and an interaction between “group” and “time” [F(1,8,58.0) = 4.0, p < .03] were found. Both groups showed a peak GH response 30 min after administration of sumatriptan (GH3). Gender, age, and IGF-1/IGFBP-3 controlled for, the ODD group had a stronger peak GH compared to the NC group [NC = 12.3 mIU/L (± 7.7); ODD = 20.9 mIU/L (± 10.9), F(1,33) = 4.9, p = .04].

In spite of a clear difference in GH responsivity between the two groups, no significant correlations were found within the NC and ODD groups separately between
the GH measures and the ratings of aggressive behavior on the CBCL or TRF.

**Methylphenidate and ADHD Comorbidity**

Next, we compared the ODD subgroups with \((n = 10)\) and without \((n = 10)\) MPH. No differences were found on baseline GH and peak GH. Furthermore, the ODD subgroup without MPH had a significantly stronger GH response 30 min after SUM administration \[22.7 \text{ mIU/L (± 11.8)}\] than the NC group \((n = 14)\) \[12.3 \text{ mIU/L (± 7.7); } U = 29, p < .02\].

In addition, no differences were found on baseline GH and peak GH between ODD subgroups with \((n = 13)\) and without \((n = 7)\) ADHD comorbidity.

**Cortisol**

With respect to CORT, six subjects (two NC and four ODD) had one or two outlier values of the six samples collected in each individual. These values were replaced by the averages of the subgroup for the sample concerned. There was no group difference at CORT1 \[F(1,34) = .80, p = .38\], nor after an hour of rest [CORT2; \(F(1,34) = 3.5, p = .07\)], but values in both groups declined between sample CORT1 and CORT2 \[F(1,33) = 18.8, p < .001\]. A repeated measures ANOVA revealed a main effect of “time” \[F(3.6,120.3) = 3.7, p = .01\], no effect of “group” \[F(1,33) = 2.6, p = .12\], and a “group by time” interaction \[F(3.6,120.3) = 4.1, p = .01\]. The significant interaction was attributable to the NC group showing a CORT response after CORT3, whereas such a response was absent in the ODD group (Figure 3).

No differences in CORT levels were found between ODD subgroups with or without MPH.

**Psychological Data**

The NC and ODD groups did not differ on any of the trait and state anxiety measures used (FSSC-R total, subscale of medical fear, STAI-C). Both groups reported to be less anxious at the end of the procedure. Also, although there was a significant time effect on the total VAS score, there was no main effect of “group” nor a “group by time” interaction.

**Discussion**

The aim of this study was to investigate the sensitivity of the 5-HT\(_{1B/1D}\) receptor in hospitalized children with ODD. To that end, the GH response to a challenge with sumatriptan, a 5-HT\(_{1B/1D}\) receptor agonist, was examined in 20 children with ODD and 15 NC children. Children with ODD had a significantly stronger GH response to sumatriptan, suggesting a heightened sensitivity of the 5-HT\(_{1B/1D}\) receptor. An augmented 5-HT activity (e.g., elevated PRL response to fenfluramine and higher levels of CSF 5-HIAA) in children with aggressive behavior has been reported before (Castellanos et al 1994; Halperin et al 1994). These results are in line with the developmental hypothesis of Halperin et al (1994) that 5-HT regulation in aggressive children develops differently than in nonaggressive children.

5-HT\(_{1B/1D}\) receptors are located both presynaptically, where they function as release-inhibiting autoreceptors, and postsynaptically (Barnes and Sharp 1999). Increases in 5-HT neurotransmission (e.g., by administration of the 5-HT precursor tryptophan, resulting in an enhanced
availability of 5-HT) has been shown to increase GH release in humans (Winokur et al. 1986). Because stimulation of 5-HT1B autoreceptors is expected to reduce 5-HT release, it is possible that sumatriptan-induced GH release is mediated via stimulation of the postsynaptic 5-HT1B/1D receptors (Whale et al. 1999). Our results may suggest a heightened sensitivity of the postsynaptic 5-HT1B/1D receptors in ODD children. Whether this enhanced sensitivity of the postsynaptic 5-HT receptors is primary or secondary to, for example, a diminished 5-HT release cannot be assessed on the basis of the current data. Lower levels of CSF 5-HIAA (Kruesi et al. 1990) and plasma 5-HIAA in children with ODD (Van Goorzen et al. 1999) fit with either interpretation. Lower 5-HIAA levels may either reflect a compensatory reduction in 5-HT release elicited by hypersensitive postsynaptic 5-HT receptors or have caused a heightened receptor sensitivity (Wetzler et al. 1991).

Although the GH response in children with ODD and NC children differed significantly, there is a number of confounding issues to be addressed. First, sumatriptan has high affinity for the human 5-HT1B and 5-HT1D receptors but also binds to the 5-HT1F receptor. Therefore, it is not possible to exclude a role of this receptor in the mechanisms underlying the observed effect on GH. Information on this receptor subtype is scarce, but preliminary data suggest a restricted distribution with low abundance (Barnes and Sharp 1999). Second, although the data of the study show that the sensitivity of the 5-HT1B/1D receptors in the pituitary–adrenal axis is elevated in children with ODD, it is not clear whether this observation can be generalized to higher brain regions, because sumatriptan does not seem to cross the blood–brain barrier easily (Sleight et al. 1990). Third, the present study did not include a placebo control challenge group. The addition of such a group could have been used to assess the effect of stress on the GH response; however, we do not believe that the stronger GH response after sumatriptan administration in the ODD group was caused by stress due to the physically aversive procedures of the study and that the ODD group suffered more from stress than NC children. Children with ODD had lower CORT levels throughout the procedure and they did not differ from the NC children on subjectively reported stress. Furthermore, if the increased CORT response found in the NC children reflects a difference in the experience of the stressor (i.e., the administration of subcutaneous sumatriptan), one should have also found a larger GH response in the NC group. Finally, 10 ODD children were being treated with MPH. Although ideally all subjects would have been off medication during the study, for clinical reasons we decided not to do this; however, there was no difference in baseline GH or GH response after sumatriptan administration between ODD children with and without MPH. We therefore do not think that the treatment with MPH can explain the present pattern of findings.

It goes without saying that the outcomes of our study should be interpreted with caution. The groups tested were relatively small and imbalanced with respect to gender. The data did, however, not show an effect of gender, age, or pubertal development on the differences in GH responsibility as established between these two groups. Furthermore, within the separate groups no significant correlations between GH responsivity and CBCL ratings of aggression were found. Studies using larger samples are needed to investigate this relationship in a more detailed way.

To our knowledge, this is the first study investigating the functionality of the 5-HT1B/1D receptor system, as reflected by the GH response to sumatriptan, in children hospitalized for ODD. In line with data from animal studies, the results suggest a role for the 5-HT1B/1D receptor in the modulation of aggressive behavior in humans, and children in particular. Further studies on the role of this receptor subtype in regulation of aggressive behavior are warranted. Prospective longitudinal studies from childhood onward are necessary to find out about the developmental course of serotonergic functioning. Finally, serotonergic challenge tests before and after pharmacologic intervention with selective serotonin reuptake inhibitors could clarify whether any positive behavioral effects are related to changes in 5-HT1B/1D receptor functioning.

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References


