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Platelet Serotonin in Newborns and Infants: Ontogeny, Heritability, and Effect of *In Utero* Exposure to Selective Serotonin Reuptake Inhibitors

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ABSTRACT

Ontogeny of platelet serotonin (5-hydroxytryptamine, 5-HT) during the first year of life was examined in newborns and infants. The effects of *in utero* exposure to selective serotonin reuptake inhibitors (SSRI, including fluoxetine, sertraline, and citalopram) were examined by comparing cord blood 5-HT levels in exposed and unexposed newborns. Heritability was assessed by correlation of the platelet 5-HT values observed for mother-infant pairs. No age effect was observed in 1–49 wk-old infants ($r = 0.13$, $p = 0.49$) and mean platelet 5-HT levels in infants (241 ± 102 ng/mL, $n = 33$; 615 ± 320 ng/10^9 platelets, $n = 32$) were similar to those reported for older children and adults. However, significantly lower blood 5-HT levels were observed in newborns (81.3 ± 32.5 ng/mL, $n = 16$, $p < 0.0001$; 297 ± 101 ng/10^9 platelets, $n = 11$, $p = 0.0007$) compared with the 1–49 wk-old infants. The mean cord blood 5-HT concentrations in newborns exposed *in utero* to SSRI ($n = 8$) were substantially lower than that seen in unexposed ($n = 16$) newborns (20.6 ± 14.4 *versus*. 81.3 ± 32.5 ng/mL, $p = 0.0001$; 90.7 ± 55.4 *versus*. 297 ± 101 ng/10^9 platelets, $p = 0.0005$). Platelet serotonin levels (ng/10^9 platelets) in mother-child pairs ($n = 32$) were significantly correlated ($r = 0.415$, $p = 0.018$). The results indicate that, although platelet 5-HT is low at birth, values quickly increase and stabilize at near-adult levels by 1 mo of age. Gestational exposure to SSRI appears to substantially reduce platelet 5-HT uptake in the fetus, strongly suggesting that such exposure has important physiologic effects. The observed mother-infant correlation agrees with a previous report of high heritability in a large adult population. **(*Pediatr Res* 56: 418–422, 2004)**

Abbreviations

5-HT, 5-hydroxytryptamine
QTL, quantitative trait loci
SSRI, selective serotonin reuptake inhibitor

There is a continuing interest in platelet serotonin (5-HT) due to its hemostatic, thrombogenic, and cardiovascular effects (1, 2), its utility in assessing the bioeffects of SSRI (3–5), and its alteration in several neuropsychiatric disorders (6–8). In prior work (9–11), we carried out a series of studies examining the effects of SSRI exposure on platelet 5-HT in nursing infants and in the present study seek to extend the available data regarding the normal ontogeny of platelet 5-HT in infants. We also wished to establish more firmly prior reports of low platelet 5-HT levels in newborn cord blood and to examine the effects of gestational SSRI exposure on cord blood levels. Finally, our investigations of nursing mother-infant pairs provided the opportunity to contribute to the limited data assessing the heritability of platelet 5-HT.

The platelet and neuronal 5-HT transporters are encoded by the same gene and appear identical in terms of pharmacology (12, 13). All platelet 5-HT is accumulated by uptake through the platelet membrane 5-HT transporter and a number of studies have used the decline in platelet 5-HT seen after administration of reuptake inhibitors as an index of central and peripheral transporter blockade (3–5). The impact of central serotonin 5-HT modulation by SSRI during critical periods of brain development is unknown. Although preclinical studies indicate that 5-HT plays important roles in neurogenesis and neural growth (14–20), it is unclear how transporter inhibition affects early neurodevelopment in humans.

Research on fetal and neonatal exposure to SSRI has been recently reviewed (10, 11, 21, 22). Although substantial and physiologically meaningful infant SSRI exposure through breast-feeding by mothers receiving SSRI is probably infre-

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quent (9–11, 23), gestational exposure has been reported to have marked biochemical effects and may have significant clinical effects (21, 22). Elucidation of the normal ontogeny of platelet 5-HT is beneficial when attempting to assess the degree of uptake inhibition in fetuses and infants of mothers receiving SSRI. Measurements in neonates may also help in understanding the role of serotonin in pregnancy and placental physiology.

Estimation of the familiality and heritability of platelet 5-HT is of interest when attempting to understand the underlying bases of group mean alterations seen in children with autism spectrum disorders (6, 7). Recent evidence suggests that adult platelet 5-HT levels are extremely heritable (24, 25). However, available heritability data in children are meager and there were no data regarding the inheritance of the measure in infants.

METHODS

Subects. Thirty-three breast-feeding mother-infant pairs were referred by their primary care provider to the Yale Behavioral Gynecology Program for evaluation and consultation regarding the treatment of postpartum depression and/or the use of antidepressants during lactation. Nursing mothers (mean age, 33.3 y; range, 23–41 y) and infants (14 males, 19 females; mean age, 18.6 wk, SD = 12.8) had blood drawn by venipuncture and heelstick, respectively, for determination of whole blood 5-HT levels *prior* to the mother's initiation of fluoxetine ($n = 12$) or sertraline ($n = 21$) treatment. Blood was obtained between 1000 and 1400 h and collected into tubes containing dipotassium EDTA. The effects of exposure to SSRI during breast-feeding have been reported for 30 of the infants (10, 11).

Cord blood samples were obtained from eight infants (four males, four females) whose mothers were referred to the Yale Behavioral Gynecology Program due to their use of SSRI during pregnancy. Mothers (mean age, 33.1 y; range, 25–41 y) of exposed infants were receiving SSRI for treatment of depression or, in one case, obsessive-compulsive disorder at the time of delivery. Five were receiving fluoxetine (10–40 mg/d), two were being treated with sertraline (50 and 75 mg/d, respectively), and one was receiving citalopram (20 mg/d). A blood sample was obtained from six of the mothers of the gestationally exposed infants. Cord blood samples were also obtained from 16 unexposed infants whose mothers gave birth at either of two local university-affiliated hospitals. Mothers of the exposed and unexposed infants were determined by their obstetrician to have had normal pregnancies and to have not used agents that might have affected platelet 5-HT levels (other than SSRI in the "exposed" group) or any psychotropic medications or substances of abuse (other than alcohol and tobacco) during pregnancy. Mothers of the exposed and unexposed groups were of similar age, socioeconomic status, and racial composition. The studies were approved by the Human Investigation Committee of Yale University School of Medicine and all mothers gave written informed consent.

Bioanalytical measurements. All specimens obtained for whole blood 5-HT analysis were initially kept at room temperature, 25 or 250 μL portions were removed and stored at −70°C; portions were also sent for automated platelet count (Hematology Laboratory, Yale-New Haven Hospital, New Haven, CT, U.S.A.). Whole-blood 5-HT levels were determined in duplicate or triplicate by HPLC with fluorometric detection as previously described (10, 26). Nearly all of blood 5-HT is located within the platelet and whole-blood 5-HT concentrations (ng/mL) can also be expressed on a per-platelet (ng/10^9 platelets) basis if a whole-blood platelet count (platelets/mL) is obtained. Even in a situation where plasma levels of free 5-HT increased 10-fold, approximately 99% of whole blood 5-HT would be found in the platelet. Plasma levels of fluoxetine, norfluoxetine, sertraline and desmethylsertraline were determined by HPLC by Princeton Biomedical Laboratories (Princeton, NJ, U.S.A.).

Statistical analyses. Group data are given as mean ± SD. *t* and Mann-Whitney *U* tests were used to test group differences depending on group size and distribution. Correlations were performed using either Pearson's *r* or Spearman's rank correlation. Most analyses were performed using both ng/mL and ng/10^9 platelets units for 5-HT concentration to facilitate comparison with previous studies; as will be discussed, the units of ng/10^9 platelets are usually preferred.

RESULTS

Ontogeny of platelet 5-HT. The mean platelet 5-HT levels in the 1–49 wk-old nursing infants were 241 ± 102 ng/mL ($n = 33$) and 615 ± 320 ng/10^9 platelets ($n = 32$) (Fig. 1). Infant blood samples were obtained before initiation of SSRI-treatment of the mothers. As shown in Figure 2, no correlation was observed between infant platelet 5-HT (ng/10^9 platelets) and age over the 1–49 wk-old age range ($n = 32$, Pearsons's $r = 0.13$, $p = 0.49$). No significant correlations were observed between age and 5-HT expressed as ng/mL ($r = -0.06$, $p =$

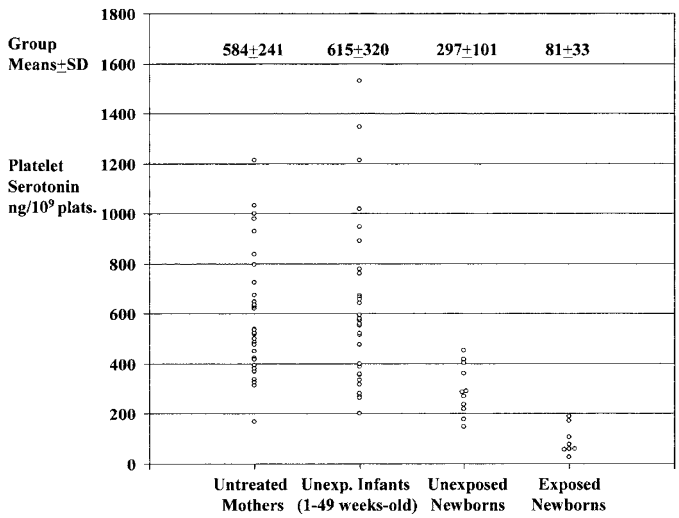

Figure 1. Individual platelet 5-HT concentrations (ng/10^9 platelets) observed for mothers of nursing infants $n = 32$), nursing infants ($n = 32$), unexposed newborns ($n = 11$), and newborns exposed *in utero* to SSRI ($n = 8$); newborn analyses were performed using cord blood samples. Group means (± SD) are given above the plotted data points.

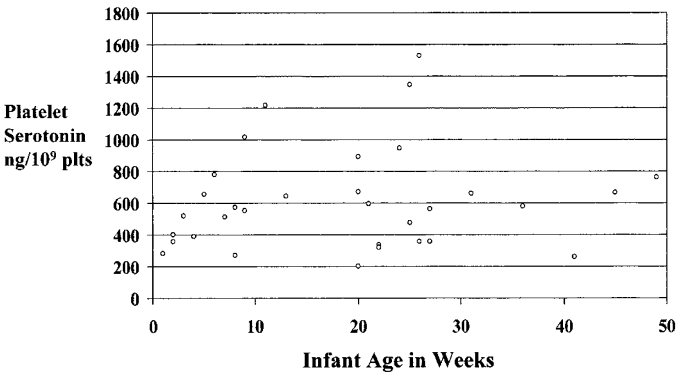

Figure 2. Infant platelet 5-HT (ng/10^9 platelets) concentrations plotted *vs* infant age in weeks ($n = 32$). No correlation was observed between 5-HT level and age ($r = 0.13$, $p = 0.49$).

0.75) or between age and infant platelet count ($r = -0.26$, $p = 0.13$).

The mean 5-HT levels observed in cord blood specimens obtained from unexposed newborns were 81.3 ± 32.5 ng/mL ($n = 16$) and 297 ± 101 ng/10^9 platelets ($n = 11$). The newborn concentrations were significantly lower (33% and 48% of the mean values seen in infants) than the values seen in the 1–49 wk-old infants (Mann-Whitney *U* test, $z = 5.3$, $p < 0.0001$ and $z = 3.4$, $p = 0.0007$, respectively; see Fig. 1). The levels in newborns ($n = 11$) also tended to be lower than the levels observed in the group ($n = 5$) of 1–4 wk-old infants (297 ± 101 *versus* 390 ± 87 ng/10^9 platelets), but the difference was not statistically significant ($z = 1.4$, $p = 0.16$); the group comparison using ng/mL units was also not significantly different.

Mean platelet 5-HT levels in the nursing mothers (all unmedicated) were 156 ± 65.3 ng/mL or 584 ± 241 ng/10^9 platelets, depending on the units of expression of concentration ($n = 33$ and 32, respectively; see Fig. 1). Levels of platelet 5-HT expressed as ng/10^9 platelets were not significantly different ($t = 0.44$, $p = 0.66$) between mothers and infants. However, maternal concentrations expressed in units of ng/mL were significantly lower than the levels seen in the 1–49 wk-old infants ($t = 5.48$, $p < 0.0001$). The divergence seen for group mean ng/mL values was due to the significantly higher platelet counts observed in the infants ($n = 32$) compared with their mothers (432 ± 137/nL *versus* 273 ± 61.2/nL , $t = 8.0$, $p < 0.0001$). It should be noted that 5-HT levels expressed as ng/mL tended to be correlated with platelet count in mothers ($r = 0.31$, $p = 0.085$), but not in the infants ($r = 0.03$, $p = 0.86$).

Effects of* in utero *SRRI exposure on platelet 5-HT. As seen in Figure 1, platelet 5-HT concentrations in cord blood specimens obtained from eight newborns exposed *in utero* to an SSRI were significantly lower than those observed in unexposed newborns (20.6 ± 14.4 *versus* 81.3 ± 32.5 ng/mL, $z = 3.80$, $p = 0.0001$; 90.7 ± 55.4 *versus* 297 ± 101 ng/10^9 platelets, $z = 3.47$, $p = 0.0005$). Mean platelet 5-HT levels in the mothers of exposed newborns with available samples ($n = 6$) were 43.2 ± 39.7 ng/mL and 233 ± 220 ng/10^9 platelets. The two mothers with the highest 5-HT values (109 and 75.8 ng/mL, other values: 16.7, 26.0, 14.1, and 17.8 ng/mL) had the two infants with the highest 5-HT values (34.4 and 49.4 ng/mL, other values: 5.0, 13.2, 17.0, 19.8, 13.0, and 13.0 ng/mL; see Fig. 1). Plasma drug and/or drug metabolite levels were available for four of the exposed infants and their mothers (two sertraline- and two fluoxetine-treated pairs). In three of the pairs, mothers' plasma drug levels were in the low end of the therapeutic range (sertraline, 26 and 24 ng/mL; fluoxetine + norfluoxetine, 78 ng/mL), with infant levels ranging from 25 to 85% of the mother's values. The one infant-mother pair with the highest plasma levels of fluoxetine + norfluoxetine (mother, 310 ng/mL; infant, 437 ng/mL), had the infant with the lowest observed platelet serotonin value (5.0 ng/mL).

Heritability of platelet 5-HT. An estimation of additive heritability (h^2) was obtained by correlation of maternal and infant 5-HT (ng/10^9 platelets) blood levels. A Pearson correlation of $r = 0.415$ ($n = 32$, $p = 0.018$) was observed, giving a heritability ($h^2 = 2r$) estimate of 0.83. When ng/mL was used as the unit of 5-HT concentration, the observed correlation was $r = 0.511$ ($n = 33$, $p = 0.0007$). A high maternal-infant correlation was also observed for platelet count ($n = 32$, $r = 0.566$, $p = 0.018$). As discussed below, the ng/10^9 platelets unit may be preferable as it accounts for familial similarities in platelet count.

DISCUSSION

The measurements of platelet 5-HT in 1–49 wk-old infants indicated that there is little developmental change in levels after the first few weeks of life. The mean levels observed in the infants are similar to those reported for children and are only slightly higher than those seen in their mothers and typically reported for adults. Given the substantially lower mean values observed in cord blood (33% and 48% of levels seen in older infants, depending upon the units), it appears that levels in newborns rapidly increase to the levels seen in older infants, children, and adults. Only a small number of 1- to 4-wk-old neonates were studied, so it is difficult to say exactly how quickly this early increase occurs. It is not clear whether the early increase in 5-HT is due to a change in the platelet's handling of 5-HT or to an increased exposure to 5-HT. There are some very limited data that suggest 5-HT platelet uptake is fully functional in newborns (27) and that the gut's production of 5-HT (as indexed by urinary 5-hydroxyindoleacetic acid) is lower in the first week of life (28). These reports suggest that the early rise may be due to increased exposure, and this would be consistent with the expected increase in gut 5-HT release as feeding begins (29–31). However, longitudinal studies examining levels of platelet, plasma, and urine 5-HT, as well as plasma and urine levels of 5-HIAA, over the first month of life are needed to clarify the time course and mechanism of the early rise in platelet 5-HT.

The platelet 5-HT ontogeny results are in good agreement with the limited prior reports of levels in newborns and infants, both in terms of the absolute levels observed and the apparent early low levels (32–36). Although most previous studies have reported 5-HT concentrations in units of ng/mL, the tendency for ng/mL values to positively correlate with platelet count, observed here and elsewhere (37), suggests that the ng/10^9

platelets unit of concentration is preferred and a greater effort should be made to use this form of expression. The positive correlation presumably results from the greater available platelet pool able to serve as a site of 5-HT sequestration in subjects with higher platelet counts.

Gestational exposure to SSRI appeared to lead to significantly lower platelet 5-HT levels, with mean levels in exposed infants 25% (ng/mL) and 34% (ng/10^9 platelets) of levels in unexposed infants. The mean 5-HT ng/mL levels observed in SSRI-exposed and unexposed infants were in excellent agreement with the means recently reported for exposed and unexposed newborns (21.5 and 68.1 ng/mL, respectively; only ng/mL units reported) by a Finnish group (21). The percentage lowering seen in 5-HT (ng/mL) in the exposed Finnish infants (31% of unexposed) differed only slightly from that observed here. The lower platelet 5-HT concentrations observed strongly suggest that SSRI-exposure results in significant inhibition of the 5-HT transporter. Based on animal studies, it is probable that a similar extent of inhibition occurs centrally and peripherally.

It is worth noting that platelet 5-HT levels are typically reduced to 5–20% of baseline levels in patients receiving clinical doses of SSRI. Thus, it appears that gestationally exposed fetuses have a bioeffect at or near that achieved in their mothers and in other SSRI-medicated patients. This similarity in bioeffect is consistent with the plasma drug levels that have been reported to occur in gestationally exposed newborns (see ref. 21 for review) and with the plasma drug levels we observed in a subset of subjects. Although the acute behavioral and long-term neurodevelopmental effects of gestational exposure are unclear, it is becoming clear that the primary pharmacological effect of the SSRIs —uptake inhibition— is usually manifest *in utero* in fetuses of mothers receiving fluoxetine or sertraline. It appears that brain extracellular levels of 5-HT increase 2- to 3-fold after SSRI administration in primate (38), presumably by reducing clearance. However, it is not clear what magnitude of increase occurs in the plasma or peripheral tissues.

The maternal-infant Pearson correlation of $r = 0.415$ observed for 5-HT (ng/10^9 platelets) was slightly lower than the theoretical maximum of $r = 0.50$ expected for a parent-child correlation of a completely additively genetically determined trait. The estimated narrow heritability ($h^2 = 2r$) of 0.84 could have been inflated due to familiality arising from shared environment; breast-feeding may increase the likelihood of this possibility. Although all subjects were Caucasian, assortative mating may also have inflated the heritability estimate. An even higher heritability ($h^2 = 1.02$) was estimated for 5-HT when using ng/mL units of concentration. The strong correlation ($r = 0.566$) observed between maternal and infant platelet counts coupled with the tendency for 5-HT ng/mL concentration to correlate with platelet count may have further inflated the heritability estimate for platelet 5-HT expressed as ng/mL. The substantial mother-infant correlation seen for platelet 5-HT agrees with a previous report of high heritability in a large adult population (24, 25), and indicates that human platelet 5-HT is highly genetically determined in both infants and adults. However, as mentioned, the use of ng/mL units in the prior study may have led to a confounding of platelet 5-HT and platelet count heritabilities. Although platelet 5-HT appears to be highly heritable, the genetic mechanisms of the inheritance are only beginning to be explored (24, 25, 39). Identification of major quantitative trait loci (QTL) for platelet 5-HT should facilitate research examining the bases of group differences reported in certain neuropsychiatric disorders.

Several limitations of the present study ought to be noted. The group of newborns exposed *in utero* to SSRI was small ($n = 8$), limiting conclusions about the magnitude of the reduction occurring during gestational exposure and about possible differences between drugs. The group effect seen was, however, quite similar to that recently observed in a Finnish study (21). Comparisons between the exposed and unexposed groups of newborns also are limited, here and elsewhere (21), by the lack of comparison groups matched for maternal disorder. Thus, some of the group difference seen might have arisen from genetic or environmental differences associated with or resulting from the mothers' psychiatric disorder or symptomatology. The calculated mother-infant correlations and heritabilities could have been inflated due to shared environment factors. Reports of platelet 5-HT being a stable trait and the similarity of the mean infant levels to adult levels tend to support the idea that similar parent-offspring correlations would be seen in older children.

In summary, although platelet 5-HT is low at birth, values appear to quickly increase and stabilize at near-adult levels within weeks of birth. Further study of this early rise may enhance understanding of early intestinal functioning and would, at the very least, provide better ontogenetic norms. Gestational exposure to SSRI appears to substantially reduce platelet 5-HT uptake in infants, strongly suggesting that such exposure has important physiologic effects. Recent reports have indicated that gestational exposure to SSRI can adversely affect neonate behavior and well being (21, 22, 40). In addition, adverse effects of the SSRI in adult patients can include nausea, diarrhea, and bruising. These reports and observations underscore the potential clinical importance of using platelet 5-HT to estimate the drugs' bioeffect in individual newborns and neonates. The high parent-offspring heritability observed here and elsewhere is encouraging in terms of identifying underlying genetic and biologic determinants of platelet 5-HT. Clarification of these factors would facilitate research in the areas mentioned above and in neuropsychiatric disorders where alterations in platelet 5-HT have been identified.

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