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PLATELET SEROTONIN STUDIES IN HYPERSEROTONEMIC RELATIVES OF CHILDREN WITH AUTISTIC DISORDER

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Summary

Platelet serotonin (5-HT) studies were conducted with 12 hyperserotonemic and 12 normoserotonemic age-, sex-, and relationship-matched relatives of autistic probands Each group consisted of 7 mothers, 4 fathers, and 1 sister of autistic children and adolescents The density (B_{max}) of platelet 5-HT_2 receptor binding sites, labelled with [^{3}H]-lysergic acid diethylamide (LSD), was significantly lower in 11 hyperserotonemic subjects compared to 12 normoserotonemic subjects (40 9 ± 13 5 fmol/mg protein, 59 6 ± 13 2, $p < 0.004$) The affinity (K_d) for [^{3}H]-LSD binding did not differ Although the density (B_{max}) of [^{3}H]-paroxetine binding did not differ between groups, there was a small difference in the affinity (K_d) of [^{3}H]-paroxetine binding (hyperserotonemic 47 6 ± 9 0 pM, normoserotonemic 54 8 ± 12 1, $p < 0.05$) There were no significant differences in platelet 5-HT uptake, or in thrombin-stimulated 5-HT release Basal, 5-HT-stimulated, and arginine-vasopressin (AVP)-stimulated inositol phosphate production, as well as basal, prostaglandin E_1 (PGE_1)-, and forskolin-stimulated cAMP production did not differ There were signficant correlations between whole blood 5-HT levels and LSD B_{max} (r_s = -0 63, N=23, $p < 0.002$) and whole blood 5-HT levels and 5-HT uptake V_{max} (r_s = 0 56, N=18, $p < 0.02$) However, [^{3}H]-LSD labelled 5-HT_2 binding and 5-HT uptake were not correlated with each other Hyperserotonemia of autism may be heterogeneous with one subgroup of subjects with increased 5-HT uptake and another subgroup with decreased 5-HT_2 binding

Investigation of serotonergic measures in autism began with a report (1) that more than 25% of children with autism had hyperserotonemia, which was defined as a whole blood 5-HT level greater than 1 67 S D above the normal control mean This finding has been extensively replicated and factors such as platelet count (2,3), platelet volume (4), and diet (5) have been excluded A normal developmental course with a decrease of whole blood 5-HT to adult levels by 7 to 9 years (6) has been demonstrated in normal humans Whole blood 5-HT levels are remarkably stable over time in normoserotonemic, adult control subjects (7)

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Since autistic disorder is most probably an etiologically heterogeneous clinical syndrome, hyperserotonemia has been of interest as a possible marker of a more homogeneous subgroup which may share either a common etiology or common pathophysiological mechanism (5) However, hyperserotonemic autistic children have symptoms which are similar to normoserotonemic autistic children (8) Recently, several studies have indicated familiality of hyperserotonemia of autism (9-12) A recent report has suggested that hyperserotonemia may be a marker of a genetic subtype of autistic disorder (13)

Since autistic disorder is a neuropsychiatric disorder without a sufficient animal model, this study used measures designed to study proteins involved in central nervous system function through use of the human platelet model (reviewed in (14)) Increased platelet 5-HT uptake and/or decreased platelet 5-HT release could lead to elevated steady state platelet 5-HT levels Signal transduction through 5-HT_2 and other receptors coupled to phospholipase C regulates both 5-HT uptake and release (15,16) cAMP dependent protein kinase regulates phospholipase C in platelets Therefore, we studied platelet [^{3}H]-LSD labelled 5-HT_2 receptor binding sites, [^{3}H]-paroxetine labelled 5-HT uptake binding sites, 5-HT uptake, inositol phosphate (a measure of phospholipase C activity) production, cAMP production, and 5-HT release This extensive set of measures was studied in hyperserotonemic first-degree relatives of children with autistic disorder compared to normoserotonemic relatives to narrow the focus of further investigations with children with autistic disorder since the parents were more able to cooperate with blood-drawing procedures designed to minimize disruption of platelets during venipuncture

Methods

Subjects

Two groups (hyperserotonemic and normoserotonemic) of 12 age- and sex-matched subjects were studied The mean age of the hyperserotonemic subjects (38 2 ± 6 7 yr) did not differ from that of the normoserotonemic subjects (38 1 ± 6 4 yr) Each group consisted of 7 mothers, 1 sister, and 4 fathers of autistic children The autistic children had all been diagnosed by DSM-III (17) or DSM-III-R (18) criteria by clinical interview of one or both parents (B L , E C) Hyperserotonemic subjects were selected from earlier studies of the familiality of hyperserotonemia (11,12) and screening of 60 parents of autistic children at the 1991 Illinois Society for Autistic Citizens annual meeting All parents who had hyperserotonemia were contacted to participate Several hyperserotonemic parents could not participate because they could not discontinue prescribed medication for the study Eleven hyperserotonemic parents were able to participate and another adult hyperserotonemic sibling was included The definition of hyperserotonemia was set at greater than 2 standard deviations above mean whole blood 5-HT levels determined in 98 consecutively ascertained blood bank donors who were not autistic and not related to an autistic proband (19) Whole blood 5-HT levels analyzed using a liquid-liquid extraction and spectophotofluorometry (7) revealed these women had whole blood 5-HT levels of 193 ± 50 ng/ml (mean ± S D) and the men had whole blood 5-HT levels of 170 ± 56 ng/ml For relatives previously assayed with this method, hyperserotonemia was defined for this study as whole blood 5-HT greater than 293 ng/ml for women or greater than 282 ng/ml for men Samples assayed since 1987 have been determined by HPLC-fluorometry (20), which is highly correlated with the spectrophotofluorometric method but which yields 0 75 fold lower values in our laboratory based on 84 samples which were assayed with both methods Therefore, hyperserotonemia using the HPLC assay in our laboratory was defined as greater than 221 ng/ml for adult females or greater than 212 ng/ml for adult males