Short report

The ontogeny of 3,4-dihydroxyphenylacetic acid in human cerebrospinal fluid

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SUMMARY Measurement of cerebrospinal fluid (CSF) levels of the minor dopamine metabolite 3,4-dihydroxyphenylacetic acid in neonates and children indicates that a rapid decline (approximately 90%) occurs in the first 2 years of life. The much less rapid ontogenetic decline seen for the predominant dopamine metabolite, homovanillic acid (HVA), indicates that differing factors affect CSF levels of the two acid metabolites. Further study is required to determine which compound more closely reflects ontogenetic changes in dopamine functioning.

Cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) have been measured widely in an effort to assess central turnover of their parent neurotransmitters, serotonin (5-HT) and dopamine (DA) respectively. Several studies of the normal ontogeny of CSF 5-HIAA and HVA levels in children have been performed in order to establish normal ranges for different ages and so that the extent of change during childhood might be estimated.\(^1\)\(^-\)\(^10\) In short, elevated levels are observed in human neonates, and age-related declines occur during childhood with the decline in CSF HVA appearing to be more extended than that seen for 5-HIAA. These findings are made more meaningful by the observation that similar age-related declines of the compounds occur in rat CSF.\(^11\)

An alternate catabolite of dopamine is 3,4-dihydroxyphenylacetic acid (DOPAC). Unlike HVA (the predominant metabolite of DA in primates), which is formed by the action of both monoamine oxidase (MAO) and catecholamine-O-methyltransferase (COMT), DOPAC is formed after MAO catabolism only. We have measured CSF levels of DOPAC in neonates and children in order to study the normal ontogeny of the compound and in the hopes of clarifying the reasons for the developmental declines seen for HVA and 5-HIAA.

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Methods

Neonatal subjects
Lumbar CSF was obtained from 46 neonates in the Newborn Special Care Nursery at Yale-New Haven Hospital. The study was approved by the Yale University Human Investigation Committee. Fluid was obtained only when a lumbar puncture was required for medical reasons. Usual complaints or indications were lethargy, apnoea, and suspected intraventricular haemorrhage (IVH) or sepsis. Subjects’ sex, weight, gestational age, one- and five-minute Apgar scores, and type of delivery were noted at the time of the spinal tap. The infants’ medical records were examined carefully for medical complications. A subgroup (n = 17) of less complicated (or normal) infants had none of the following signs: IVH, seizures, asphyxia, hydrocephaly, five-minute Apgar score less than 5, sepsis, or CNS medications. The mean (SD) gestational age in this less complicated group was 37±1 (4-2) weeks, and the mean birth weight was 2711 (1150) g (range 4270 to 1000). Fourteen specimens (those of sufficient volume) were analysed for DOPAC.

Childhood subjects
Lumbar CSF was obtained for diagnostic purposes from patients with acute lymphoblastic leukaemia (ALL) in the Yale-New Haven Medical Center Pediatric Clinic. From this population patients were selected who were in first complete remission and without clinical evidence of neurological disease or complications of therapy. To exclude acute and subacute changes resulting from induction treatment and CNS prophylaxis, CSF specimens from the first 150 days of therapy were excluded, as were samples obtained after a relapse or from subjects with clinical evidence of neurological disease. Some patients were receiving maintenance chemotherapy consisting of daily oral 6-mercaptopurine
(6-MP) and weekly oral methotrexate, with or without oral cyclophosphamide. The childhood subjects are described in more detail in an earlier publication.6

Analysis

CSF samples (200 μl) were prepared for analysis using an alumina extraction procedure similar to that used for brain and plasma samples.12 Samples were analysed electrochemically following chromatography on a 25 x 0.46 cm Ultrasphere 5u C18 reverse phase column using a mobile phase (1-0 ml/min) of pH 3.5 0.1M phosphate buffer containing 100 mg/l of sodium octylsulfate and 15% methanol. Typical retention times for dihydroxybenzylamine (the internal standard-DHBA) and DOPAC were 8.4 and 12.8 minutes, respectively. Absolute detection limits were 5–10 pg, giving concentration detection limits of 0.1–0.3 ng/ml of CSF. Concentrations were corrected for the consistently lower recoveries observed for DOPAC relative to DHBA.

Results

Group means and individual data are presented in the fig. The group mean (SD) CSF DOPAC concentration in the neonates (3.58 (1.71) ng/ml, n = 14) was significantly (p < 0.0001) higher than that seen in the 3–10 year-old children (0.32 (0.27) ng/ml, n = 20). Because of the high relative standard deviations, the group means also were calculated on log-transformed data. After log transformation, group means (SD) of 3.35 (1.41) ng/ml and 0.22 (0.14) ng/ml were calculated in the neonatal and childhood groups. The groups were different at the p < 0.0001 level.

Data from the 3–10 year-old children were grouped together, as no age-effect was observed over that age range (r = 0.18, p = 0.55). The age-effect also was examined within the neonatal group by correlating DOPAC concentration with gestational age at the time of the lumbar puncture. No correlation with age (r = 0.06, p = 0.79) was observed over the 30–43 week gestational age range examined.

Discussion

It is apparent from these first reported measurements of CSF DOPAC in neonates and children that CSF DOPAC levels decrease markedly in early childhood. The decline appears more abrupt than for 5-HIAA or HVA, as children of 3–4 years of age already display levels similar to those observed in adults.13 14 In this regard, the ontogeny of DOPAC is most like that of MHPG,1 4 although no correlation with age was seen over the 30–43 week gestational age range. As described in Methods, care was taken to minimise the effect of illness and treatment on the in-remission leukaemic subjects. Age-group means observed for 5-HIAA and HVA for such patients6 were similar to those previously reported for various neurological control groups, indicating that the levels and ontogeny observed for CSF DOPAC in the in-remission leukaemias probably are similar to those seen in normal children.

It is not clear whether the rapid decline seen for CSF DOPAC and the more extended decline reported for HVA (see above) are a reflection of brain levels of the compounds. Although there is evidence from animal studies suggesting that ontogenetic changes in CSF HVA parallel changes in brain levels,11 there are few data regarding the relationship of brain and CSF DOPAC. Studies examining the ontogeny of DOPAC in rat brain have actually observed developmental increases.15 16 The measurement of brain and CSF DOPAC (and HVA) in developing primates would do much to answer the question concerning brain-CSF relationships in humans.

At present, one can only speculate concerning the possible utility of CSF DOPAC levels in assessing dopamine functioning in children. There is some indication that the information derived from DOPAC measurements may be distinct from, and complementary to, that obtained from the measurements of CSF HVA. The very different profiles seen in the declines of DOPAC and HVA suggest that an increase in efflux mechanisms common to both compounds (such as increased bulk flow of CSF or increased acid transport) probably is not responsible for the declines.

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