Reduced Brain Delivery of Homovanillic Acid to Cerebrospinal Fluid During Human Aging

Stanley I. Rapoport, MD; Mark B. Schapiro, MD; Conrad May, MD

Background: Markers of human brain dopamine metabolism are reported to decline with age. However, the cerebrospinal fluid (CSF) concentration of homovanillic acid (HVA), a major dopamine metabolite, is reported to not change or to increase in elderly individuals.

Objective: To estimate the rate of delivery of HVA from the brain to CSF, taking into account the HVA concentration gradient in the spinal subarachnoid space and CSF flow.

Methods: Homovanillic acid concentrations were measured in 5 serial 6-mL aliquots of CSF removed from the L3-4 or L4-5 interspaces of 7 healthy young (mean±SD age, 28.7±4.6 years) subjects and 7 healthy elderly (mean±SD age, 77.1±6.3 years) subjects. Cisterna magna HVA concentrations were estimated from the slopes of the HVA concentrations along the spinal subarachnoid space. The products of cisternal HVA concentrations and published values for CSF flow were used to estimate lower limits for brain delivery of HVA to CSF, according to the Fick principle.

Results: The mean±SD HVA concentration in the initial lumbar CSF sample in the young subjects, 116±66 pmol/mL, did not differ significantly from 140±86 pmol/mL in the elderly subjects. Estimated cisternal HVA concentrations equaled 704 and 640 pmol/mL, respectively, in the young and elderly subjects. Multiplying these concentrations by CSF flow rates of 591 and 294 mL/d, respectively, gave lower limits for rates of delivery of HVA from the brain to CSF. These rates equaled 416 and 175 nmol/d, respectively.

Conclusion: A 50% decline in the lower limit for the rate of HVA delivery from the brain to CSF in elderly individuals is consistent with other evidence that brain dopaminergic neurotransmission declines with age.

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young and elderly subjects, when taking into account published values for F and new values for lumbar CSF concentration of HVA.

The Figure presents mean values for HVA concentration in the five 6-mL CSF aliquots that were removed serially from the 7 young and 7 elderly subjects. A repeated analysis of variance demonstrated a statistically significant relation between HVA concentration and aliquot number (P = .001) but an insignificant difference in mean HVA concentration in any aliquot between the 2 groups. In the young and elderly subjects, mean±SD HVA concentration in the initial (caudal) 6-mL aliquot equaled 116 ± 56 and 140 ± 84 pmol/mL, respectively (Table). The mean±SD slopes of plots of HVA concentration against aliquot number, 39.2 ± 2.4 and 33.3 ± 3.4 pmol/mL per aliquot for young and elderly subjects, respectively, did not differ significantly (P > .05).

Table. Calculations of Rates of Homovanillic Acid (HVA) Transfer by Cerebrospinal Fluid (CSF) Bulk Flow From the Cisterna Magna to the Spinal Subarachnoid Space and Out of the Spinal Subarachnoid Space at the Lumbar Level

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Young Subjects</th>
<th>Elderly Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentrations and slopes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measured lumbar CSF HVA concentration, mean ± SD, pmol/mL</td>
<td>116 ± 56</td>
<td>140 ± 84</td>
</tr>
<tr>
<td>Calculated spinal subarachnoid HVA concentration gradient, mean ± SD, pmol/mL per 6-mL fraction†</td>
<td>39.2 ± 2.4</td>
<td>33.3 ± 3.4</td>
</tr>
<tr>
<td>Cerebral subarachnoid HVA concentration, pmol/mL‡</td>
<td>704</td>
<td>640</td>
</tr>
<tr>
<td>F, mL/d‡</td>
<td>591</td>
<td>274</td>
</tr>
<tr>
<td>HVA bulk flow transfer rates, nmol/d</td>
<td>416</td>
<td>175</td>
</tr>
<tr>
<td>Cerebral subarachnoid space to spinal subarachnoid space†</td>
<td>69</td>
<td>38</td>
</tr>
<tr>
<td>Rates of outward HVA transport, nmol/d</td>
<td>347</td>
<td>137</td>
</tr>
<tr>
<td>From spinal subarachnoid space§</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: F, CSF flow rate.
†Calculated by linear regression from relation in the Figure between CSF HVA concentration and aliquot number.
§Estimated cisterna magna HVA concentration from slope, assuming 96 mL of spinal subarachnoid CSF.
¶Cisterna magna HVA concentration ÷ F.
||First aliquot of lumbar HVA concentration ÷ F. (cisterna magna HVA concentration – caudal aliquot spinal subarachnoid HVA concentration).

Under an institutional review board–approved protocol, we studied 7 healthy young adults (mean±SD age, 28.7±4.6 years; range, 21–26 years; 3 men and 4 women) and 7 healthy elderly adults (mean±SD age, 77.1±6.3 years; range, 67–84 years; 5 men and 2 women), who had not taken off any medication for at least 2 weeks. Each subject was medically screened with a physical examination and routine blood tests and was in excellent health. Cerebrospinal fluid flow rates have been reported for these subjects. Flows have been reported to fall by about 50% in these elderly subjects compared with the young subjects, from 591 to 274 mL/d (Table). Flows measured by intraventricular infusion also have been reported to decline, from 720 mL/d at 29 years of age to 403 mL/d at 79 years of age.

We multiplied the values for F in the Table by the corresponding cisternal HVA concentration to calculate HVA transfer rates by CSF flow from the cisterna magna to the spinal subarachnoid space. These rates equaled 416...
and 175 nmol/d, respectively (Table). We also calculated HVA outflow rates from the L3-4 or L4-5 lumbar spaces as the product of $F$ and HVA concentration in the most caudal lumbar aliquot. These rates equaled 69 and 38 nmol/d, respectively, in young and elderly subjects (Table). The differences between the outflow and inflow rates equaled 347 and 137 nmol/d, respectively. They represent, according to the Fick principle, rates of removal of HVA from the spinal subarachnoid CSF.

We calculated that the rate of transfer of HVA via CSF flow, from the cisterna magna to the spinal subarachnoid space, falls by about 50% with age, from 416 to 175 nmol/d. According to the Fick principle, these latter rates are “lower limits” for HVA delivery from the brain to CSF. They ignore any HVA loss from CSF at the choroid plexus and subarachnoid membranes by an outward short-chain fatty acid transporter and by bulk flow into the sagittal sinus through cranial subarachnoid villi. Additionally, we estimated that HVA is removed from the spinal subarachnoid space before CSF reaches the L3-4 or L4-5 interspaces at rates of 347 and 137 nmol/d in young and elderly subjects, respectively (Table). This removal can involve outward transport by the fatty acid transporter at the spinal cord or outflow of CSF via spinal subarachnoid villi.

Our analysis, which suggests that HVA diffusion from the brain (mainly the basal ganglia and frontal cortex) into CSF falls by half with age, can explain the discrepancy between reports of reduced brain dopaminergic function but not of lumbar CSF concentrations of HVA in elderly individuals. In this regard, our measured HVA concentrations in the initial lumbar CSF samples from the young and elderly groups, 116±56 pmol/mL and 140±84 pmol/mL, respectively, are in the range of published concentrations.

Our results remain to be validated, because they are based on a number of assumptions and on data from a small number of subjects. We extrapolated a linear concentration gradient along a 96-mL spinal subarachnoid space from the concentrations in the 5 aliquots removed but our cisternal HVA concentration calculated in this way agrees with published values. It is unlikely that our results were markedly affected by non-HVA dopamine metabolites in CSF, which represent only 12% of the HVA concentration, or by diurnal changes in CSF flow, which are only plus or minus 20%. Future studies should involve larger numbers of subjects and correlated measurements, if possible, of $F$ and HVA concentrations in lumbar and/or lateral ventricle CSF.

Multiplying a known lateral ventricle HVA concentration by $F$ would give a more realistic lower bound for HVA delivery by the brain than multiplying cisternal HVA concentration by $F$.

Measured urinary HVA excretion rates and carotid-jugular HVA concentration differences suggest that the net rate of HVA production by the brain in young adults is 5.4 to 7.0 nmol/d. This rate is 13 to 17 times higher than our estimated lower limit of 416 nmol/d (Table). Thus, although cisternal HVA concentration $\times F$ reflects brain dopamine metabolism, this product represents at most 5% to 10% of the actual rate of HVA production by the brain. The remaining HVA produced, 90% to 95% of the net, likely is transported by a short-chain fatty acid transporter directly from the brain to the blood at the cerebral capillaries or from CSF at the choroid plexus or transferred by bulk flow via cranial arachnoid villi.

In summary, the product of cisternal HVA concentration or, for that matter, of lumbar HVA concentration, and of CSF flow $F$ is more useful for evaluating brain dopamine metabolism than is lumbar HVA concentration alone. This conclusion applies to aging as well as to a brain in which CSF flow is altered. For example, lumbar HVA concentrations in patients with Alzheimer disease are reported to equal or exceed control concentrations but CSF flow appears reduced in this condition. Similar considerations may apply to Parkinson disease. More generally, our results suggest that neglecting CSF flow differences in aging or disease can lead to an incorrect interpretation of the physiological or biochemical significance of measured CSF concentrations of substances derived from the brain.

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