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Discussion

Sensitivity and specificity of urinary N-acetyldopamine as a marker for neuroblastomas: comparison with traditional urinary catecholamine metabolites

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We would like to comment on the paper by Jouve *et al.* [1], who suggested that the determination of N-acetyldopamine (NADA) may provide complementary information in the diagnosis of "non-secreting neuroblastomas". The latter were defined as tumours that "do not secrete the usual catecholamines, vanillylmandelic acid (VMA), homovanillic acid (HVA), norepinephrine, epinephrine and dopamine (DA), but only L-3,4-dihydroxyphenylalanine (L-DOPA) and its metabolite vanillyllactic acid (VLA)".

The authors seem to have overlooked the fact that L-DOPA production and secretion lead to subsequent formation of HVA, in addition to other metabolites that may derive from both L-DOPA and DA, in the body. Proof can be found, *e.g.* in Parkinsonian patients treated with L-DOPA, notably when it is combined with a peripheral decarboxylase inhibitor [2–4]. In addition to formation via DA (aromatic L-amino acid decarboxylase is an almost ubiquitous enzyme in the body), HVA production from L-DOPA takes place via 3-methoxy-4-hydroxyphenylpyruvic acid (VPA), which is formed by 3-O-methylation (COMT) and transamination or L-amino acid oxidation (Fig. 1). VPA (an α-keto acid) can spontaneously, and possibly enzymatically, decarboxylate to HVA and is in fact the precursor of the metabolite VLA (via lactate dehydrogenase; not monoamine oxidase) that they considered of diagnostic importance. This means that merely L-DOPA-secreting neuroblastomas, if existent, lead to the excessive production of at least one of the "usual" catecholamine metabolites (HVA) that will be detected by the methods that are commonly used in clinical chemical laboratories. The sensitivity (number of true positives) for HVA as a marker for neuroblastomas increases when urines are incubated (*e.g.*, for enzymatic deconjugation) prior to extraction, as this promotes spontaneous decomposition of excreted VPA to HVA [3].

The true non-secreting neuroblastomas, *i.e.*, tumours that lack tyrosine hydroxylase (about 10%), are characterized by the absence of any production of compounds in the catecholamine pathway. NADA measurements will not contribute to their detection either.

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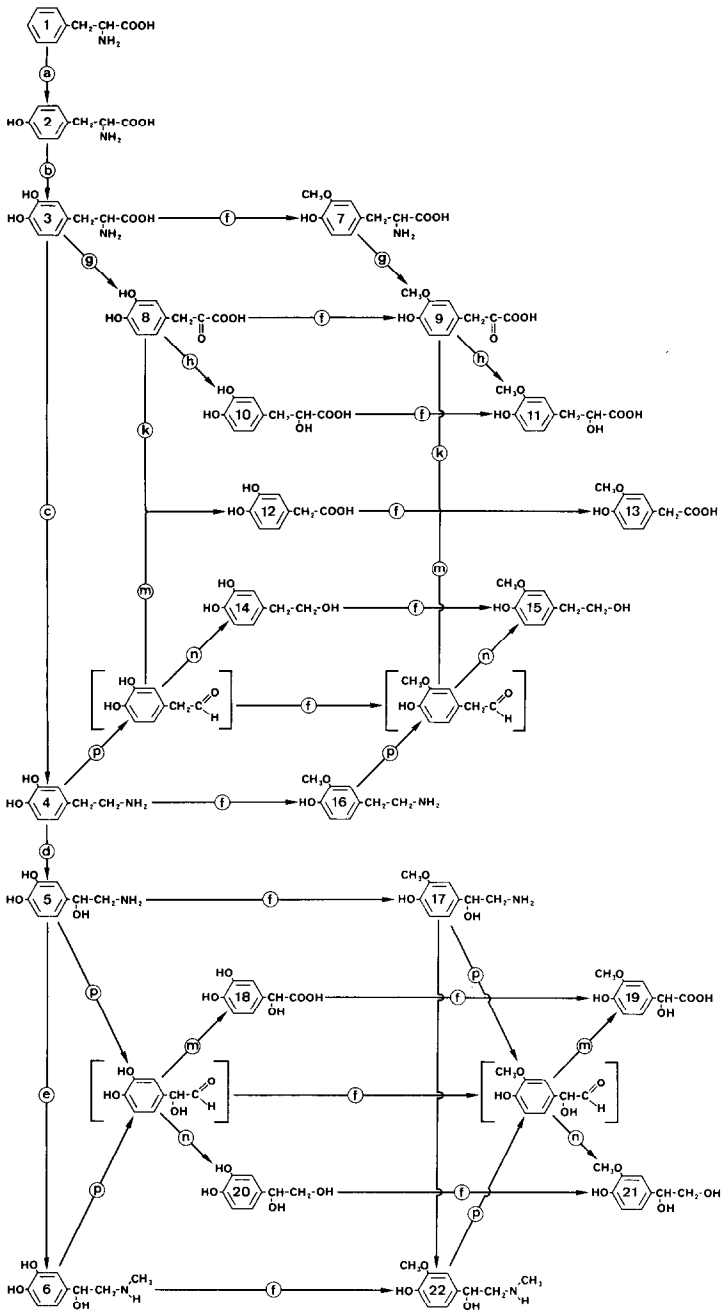

Fig. 1. Synthetic and degradative pathways in the metabolism of catecholamines. 1 = Phe, phenylalanine; 2 = Tyr, tyrosine; 3 = L-DOPA, 3,4-dihydroxyphenylalanine; 4 = DA, dopamine; 5 = NE, norepinephrine; 6 = E, epinephrine; 7 = 3MTyr, 3-methoxytyrosine; 8 = CPA, catecholpyruvic acid; 9 = VPA, vanillylpyruvic acid; 10 = CLA, catecholactic acid; 11 = VLA, vanillyllactic acid; 12 = DOPAC, 3,4-dihydroxyphenylacetic acid; 13 = HVA, homovanillic acid; 14 = DOPET, 3,4-dihydroxyphenylethanol; 15 = MOPET, 3-methoxy-4-hydroxyphenylethanol; 16 = 3MT, 3-methoxytyramine; 17 = NM, normetanephrine; 18 = DOMA, 3,4-dihydroxyphenylmandelic acid; 19 = VMA, vanillylmandelic acid; 20 = DOPEG, 3,4-dihydroxyphenylethylene glycol; 21 = MOPEG, 3-methoxy-4-hydroxyphenylethylene glycol; 22 = M, metanephrine. [ ] = Intermediate aldehyde; catechol = 3,4-dihydroxyphenyl; vanillyl = 3-methoxy-4-hydroxyphenyl. a = Phenylalanine hydroxylase; b = tyrosine hydroxylase; c = aromatic-L-amino acid decarboxylase; d = dopamine β-hydroxylase; e = phenylethanolamine-N-methyltransferase; f = catechol-O-methyltransferase; g = L-amino acid oxidase and/or tyrosine aminotransferase; h = lactate dehydrogenase; k = pyruvate decarboxylase and/or spontaneously; m = aldehyde dehydrogenase; n = alcohol dehydrogenase; p = monoamine oxidase.

Moreover, the high number of false-positive results of NADA in nephroblastoma cases is striking and a matter of undiscussed concern. This is of importance in view of the possible differential diagnostic impact of urinary catecholamine metabolite measurements, prior to the definitive pathological anatomical diagnosis, when clinicians are confronted with a child that bears an abdominal mass in the kidney region. Nephroblastomas do not cause false-positive results when the "usual" catecholamine metabolites are determined, and it is unfortunate that these metabolites and free DA were not additionally given in Table IV to allow a fair comparison of their sensitivities and specificities with those of NADA.

We conclude that NADA does not provide any information in true non-secreting neuroblastoma cases. It may provide superfluous complementary information in the hypothetical merely L-DOPA-secreting neuroblastomas and produce false-positive results in the diagnosis of classical functional neuroblastomas. Finally, when expressed in terms of creatinine, it is inadvisable to define a single reference range for children aged 0–15 years. Urinary creatinine excretion increases rapidly in the first years of life, which gives rise to a pronounced falsely age-dependent fall (a factor of 2–4) of catecholamine metabolites in this age range. Evaluation with a reference range of 0–15 years will reduce the sensitivity for the detection of functional neuroblastoma in the older children.

REFERENCES

1. J. Jouve, J. Herault, H. Tournade and J. P. Muh, *J. Chromatogr.*, 574 (1992) 9.
2 M. Sandler, R. D. Johnson, C. R. J. Ruthven, J. L. Reid and D. B. Calne, *Nature (London)*, 247 (1974) 364.
3 F. A. J. Muskiet, H. J. Jeuring, A. W. Teelken, B. G. Wolthers and J. P. W. F. Lakke, *J. Neurochem.*, 31 (1978) 1283.
4 F. A. J. Muskiet, D. C. Fremouw-Ottevangers, G. T. Nagel, B. G. Wolthers and J. A. de Vries, *Clin. Chem.*, 24 (1978) 2001.