Monoamine oxidase A down-regulation contributes to high metanephrine concentration in pheochromocytoma

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CONTEXT
The high diagnostic performance of plasma-free metanephrines (metanephrine and normetanephrine) (MN) for pheochromocytoma (PHEO) results from the tumoral expression of catechol-O-methyltransferase (COMT), the enzyme involved in O-methylation of catecholamines (CAT). Intriguingly, metanephrine, in contrast to epinephrine, is not remarkably secreted during a stress in hypertensive or normotensive subjects, whereas in PHEO patients CAT and MN are both raised to high levels. Because epinephrine and metanephrine are almost exclusively produced by the adrenal medulla, this suggests distinct CAT metabolism in chromaffin cells and pheochromocytes.

OBJECTIVE
The objective of the study was to compare CAT metabolism between adrenal medulla and PHEO tissue regarding related enzyme expression including monoamine oxidases (MAO) and COMT.

DESIGN
A multicenter comparative study was conducted.

STUDY PARTICIPANTS
The study included 21 patients with a histologically confirmed PHEO and eight adrenal glands as control.

MAIN OUTCOME MEASURES
CAT, dihydroxyphenol-glycol, 3,4-dihydroxyphenylacetic acid, and MN were measured in adrenal medulla and PHEO tissue. Western blot, quantitative RT-PCR and immunofluorescence studies for MAOA, MAOB, tyrosine hydroxylase, dopamine β-hydroxylase, L-amino acid decarboxylase, and COMT were applied on tissue homogenates and cell preparations.

RESULTS
At both the protein and mRNA levels, MAOA and COMT are detected less often in PHEO compared with adrenal medulla, conversely to tyrosine hydroxylase, L-amino acid decarboxylase, and dopamine β-hydroxylase, much more expressed in tumor tissue. MAOB protein is detected less often in tumor but not differently expressed at the mRNA level. Dihydroxyphenol-glycol is virtually absent from tumor, whereas MN, produced by COMT, rises to 4.6-fold compared with adrenal medulla tissue. MAOA down-regulation was observed in 100% of tumors studied, irrespectively of genetic alteration identified; on the other hand, MAOA was strongly expressed in all adrenal medulla collected independently of age, gender, or late sympathetic activation of the deceased donor.

CONCLUSION
High concentrations of MN in tumor do not only arise from CAT overproduction but also from low MAOA expression, resulting in higher substrate availability for COMT.

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