Riccardo Montioli Brief:

Title

Biochemical advances in AADC deficiency: an approach to understand the molecular pathogenesis of heterozygous patients and protein engineering for the enzyme replacement therapy.

Summary of presentation

Until now, only the molecular effects of homozygous mutations of the DDC were analyzed. However, although several heterozygous carriers of AADC deficiency were identified, the molecular aspects of their enzymatic phenotypes are not yet investigated. We focused our attention on the R347Q and R358H mutations because both have been found in homozygous patients and are born together by compound heterozygous patients. We purified in recombinant form either the R347Q and R358H homodimeric variants or, for the first time, the R347Q/R358H heterodimeric variant of DDC. The comparison of the biochemical features of the heterodimer with those of the relative homodimers provided evidence for a positive interallelic complementation between the R347Q and the R358H mutations. Our findings shed some light on the molecular complexity of the heterozygous condition revealing that the enzymatic phenotype of a combined heterozygous patients could exhibit features substantially different from those are expected. A second project we have recently undertaken concerns the engineering of the human DDC in order to move the first steps toward an enzyme replacement therapy of AADC deficiency. In the first place our efforts are aimed to fix the enzyme “weaknesses” to achieve a more stable and active variant of AADC that will be employed in the development of a delivery strategy.