

Title:

Reduced availability of brain amines during critical phases of postnatal development in a genetic mouse model of cognitive delay

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Text:

OBJECTIVE: Serotonin (5-HT), dopamine (DA) and noradrenaline (NE) play important roles in brain postnatal maturation. Therefore, deficits in brain availability of biogenic amines during critical developmental phases might underlie neurodevelopmental disturbances associated with cognitive impairment.

PATIENTS AND METHODS: To test this hypothesis we evaluated brain availability of 5-HT, DA and NE, of their immediate precursors 5-hydroxytryptophan and 3,4-dihydroxy-l-phenylalanine, and of large neutral amino acids phenylalanine, tyrosine and tryptophan, in developing PahEnu2 mice, the genetic model of Phenylketonuria (PKU) a cause of severe cognitive delay.

RESULTS: We found deficits of brain amine levels in PKU pups between day 14 and 35 of postnatal life, when pups of the healthy background showed developmental peak increases of amines and precursors. 5-HT deficits were most pronounced, were unrelated with brain availability of the aminoacid precursor tryptophan, but overlapped with peak brain phenylalanine concentrations and reduced availability of 5-HT direct precursor 5-hydroxytryptophan.

CONCLUSIONS: These results identify a critical window of brain amine availability susceptible to disturbances in a genetic mouse model of pathological neurodevelopment and suggest a mechanism of interference with brain aminergic synthesis in PKU and non-PKU hyperphenylalaninemia.