Positron emission tomographic studies on aromatic L-amino acid decarboxylase activity in vivo for L-dopa and 5-hydroxy-L-tryptophan in the monkey brain

P. Hartvig 1, J. Tedroff 2, K. J. Lindner 1, P. Bjurling 3, C.-W. Chang 3, H. Tsukada 3, 4, Y. Watanabe 3, 5, and B. Långström 3

1 Hospital Pharmacy, 2 Department of Neurology, University Hospital, and 3 Uppsala University PET Center, Uppsala University, Uppsala, Sweden 4 Central Research Laboratory, Hamamatsu Photonics Shizuoka, and 5 Department of Neuroscience, Osaka Bioscience Institute, Osaka, Japan

Accepted June 22, 1993

Summary. The regional brain kinetics following 5-hydroxy-L-(β-11 C)tryptophan and L-(β-11 C)DOPA intravenous injection was measured in twelve Rhesus monkeys using positron emission tomography (PET). The radiolabelled compounds were also injected together with various doses of unlabelled 5-hydroxy-L-tryptophan or L-DOPA. The radioactivity accumulated in the striatal region and the rate of increased utilization with time was calculated using a graphical method with back of the brain as a reference region. The rate constants for decarboxylation were 0.0070 ± 0.0007 (S. D) and 0.0121 ± 0.0010 min⁻¹ for 5-hydroxy-L-(β-11 C)tryptophan and L-(β-11 C)DOPA, respectively. After concomitant injection with unlabelled 5-hydroxy-L-tryptophan, the rate constant of 5-hydroxy-L-(β-11 C)tryptophan decreased dose-dependently and a 50 percent reduction was seen with a dose of about 4 mg/kg of unlabelled compound. A decreased utilization rate of L-(β-11 C)DOPA was seen only after simultaneous injection of 30 mg/kg of either L-DOPA or 5-hydroxy-L-tryptophan. This capacity limitation was most likely interpreted as different affinity of the striatal aromatic amino acid decarboxylase for L-DOPA and 5-hydroxy-L-tryptophan, respectively.

Keywords: 5-Hydroxy-L-(β-11 C)tryptophan, L-(β-11 C)DOPA, positron emission tomography, aromatic amino acid decarboxylase, monkeys

Introduction

Aromatic amino acid decarboxylase (AADC) catalyzes the decarboxylation of a wide range of aromatic amino acids, including 5-hydroxy-L-tryptophan and...
L-DOPA (Lovenberg et al., 1962; Christenson et al., 1970). In the serotonin synthesis, AADC catalyzes the transformation of 5-hydroxy-L-tryptophan to serotonin by removing carbon dioxide, a reaction first reported by Holtz (1939). The enzyme is widely distributed in mammalian tissues, and in the brain AADC seems to be localized in neuronal as well as in non-neuronal cells (Lovenberg et al., 1962; Christenson et al., 1970).

AADC is present in the brain in far greater excess than tryptophan hydroxylase (Ichiyama, 1970). The enzyme is supposed not to be rate-limiting for monoamine synthesis and is not assumed to be modulated by the neuronal activity. The Michaelis-Menten constant of the enzyme has been measured several orders of magnitude higher than the concentration of endogenous precursors (Sourkes, 1977). Recent studies, however, have disputed this statement and a much lower value was recently reported for 5-hydroxy-L-tryptophan (Siow and Dakshinamurthi, 1990).

Positron emission tomography, PET, has made possible the quantitation of selective cumulation of 5-hydroxy-L-tryptophan and L-DOPA radiolabelled with 11 C in the β-position in the striatum of Rhesus monkeys (Tedroff et al., 1992a; Hartvig et al., 1991). The rate of radioactivity accumulation shown with PET mainly represents the formation rate of (11 C)-serotonin or (11 C)-dopamine, respectively. This statement was supported by no striatal cumulation of radioactivity when the precursor radiolabelled in the carboxylic group was administered (Korf et al., 1977; Tedroff et al., 1992; Hartvig et al., 1991). Furthermore, pretreatment of monkeys with a centrally active decarboxylase inhibitor before 5-hydroxy-L-(β-11 C)-tryptophan (Hartvig et al., 1991) or L-(β-11 C)-DOPA (Tedroff et al., 1992a) had been administered, did not yield any striatal accumulation of radioactivity. The fractional decarboxylation rate of 5-hydroxy-L-tryptophan and L-DOPA radiolabelled with 11 C was calculated using a brain reference region. This directly gives the fractional decarboxylation rate in the striatum, as previous studies have shown that radiolabelled metabolites did not significantly influence the calculated rate constants (Tedroff et al., 1992a; Hartvig et al., 1991; Miwa et al., 1992). The decarboxylation rate measured in vitro has also been shown similar to the decarboxylation rate of the L-DOPA analogue 6-(18 F)fluoro-L-DOPA measured with PET (Gjedde et al., 1991). A positive identification of formed 11 C-neurotransmitter has also been achieved in the rat brain using microdialysis and brain homogenates (Miwa et al., 1992).

The aims of the present study were to assess by positron emission tomography the in vivo regulation of the decarboxylation of the two neurotransmitter precursors, i.e., 5-hydroxy-L-tryptophan and L-DOPA, radiolabelled with 11 C and to measure differences in enzyme activity for the two substrates. A mass effect on enzyme activity was also studied using various concentrations of the substrates.