《招待講演 7 》

Assessing Dopaminergic Neurotransmission in Vivo by Brain Imaging

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The main elements of dopaminergic neurotransmission in the mammalian brain include 1) transport of tyrosine from blood to brain, across the blood-brain barrier, 2) hydroxylation of tyrosine to DOPA by tyrosine hydroxylase, 3) decarboxylation of DOPA to dopamine by DOPA decarboxylase, 4) transport of dopamine into vesicles, 5) release of vesicular contents into synaptic clefts, 6) binding of dopamine to several types of receptors, pre- and postsynaptic, 7) transport of dopamine into the dopaminergic terminals, 8) metabolism of dopamine by monoamine oxidases and catechol-O-methyltransferase, and 9) diffusion of dopamine metabolites from the brain.

Some of these steps can now be assessed quantitatively in the living human brain by means of radiolabeled tracers. Tyrosine transport from blood to brain has been quantitated in healthy individuals and patients with schizophrenia with the aid of labeled tyrosine (Wiesel et al. 1992). Tyrosine hydroxylation has not been determined because of the lack of a suitable tracer. Labeled alpha-methyl-*p*-tyrosine has been shown not to have the kinetic properties necessary for the imaging of enzyme sites or activities. DOPA decarboxylation has been imaged extensively with labeled DOPA analogs such as FDOPA , the results to be presented below. Dopamine transport into vesicles has not been assessed yet, although plasma membrane transporter ligands may in some cases also bind to vesicle transporters. Dopamine binding to D_1 and D_2 receptors has been quantitated with several radioligands, notably the Schering experimental drug SCH-23,390 (D_1), the neuroleptic spiperone in several configurations (D_2), and the labeled benzamide raclopride (D_2). The plasma membrane transporter (re-uptake site) has recently been studied with labeled nomifensine, cocaine, and the Winthrop-Sterling experimental drug WIN-35,428 in several configurations (CFT, CIT). The number of binding sites of monoamine oxidase B has been determined with labeled Deprenyl but COMT still eludes study because of a suitable tracer. The diffusion of dopamine metabolites has recently been assessed indirectly by Kuwabara et al. (1993).

In many of the studies listed above, quantitation has consisted only in the determination of non-specific uptake constants but in some studies, actual transport or enzyme activities, and numbers of binding sites have been calculated. It is the latter physiological and neurochemical estimates that concern us.

The first of the biochemical steps listed above to be properly quantitated was DOPA decarboxylase activity. With a mathematical model of the relationship between the radioactivity recorded in brain tissue and the circulation, we estimated the activity of the decarboxylating enzyme (Gjedde et al. 1991, Kuwabara et al. 1993). The measurements of the relative rates of efflux (k_2) and decarboxylation (k_3) revealed almost equal rates in the striatum, approximately $4\ h^{-1}$ or $0.067\ min^{-1}$. In Parkinson's disease at Hoehn and Yahr stage 3–4, the DOPA decarboxylase activity is reduced by 50–60% in the putamen.

During a search for abnormalities of catecholaminergic neurotransmission in the amygdaloid nuclei of patients with complex partial seizures of mesial temporal lobe origin, we unexpectedly discovered an increase of the DOPA decarboxylase activity of the striatum of a subgroup of patients with a history of psychotic symptoms. When specifically assayed for the same abnormality, a group of patients with schizophrenia revealed a significant increase of the enzyme in the striatum. The finding corroborates the view that schizophrenia is essentially a dopamine deficiency disorder.

The possible upregulation of DOPA decarboxylase activity in schizophrenia, explained as a consequence of decreased excitation of the nigrostriatal pathway, and

associated with reduced baseline or tonic firing of dopaminergic neurons, may have a counterpart in the postulated upregulation of dopamine D_2 receptors in the striatum. Both of these changes would be expected to increase the sensitivity of striatal neurons to burst firing, believed to be the physiological basis for dopamine surges (release).

Supported by MRC (Canada) (SP-5, PG-41, SP-30), Lundbeck Foundation (Copenhagen), Low-Beer Family Foundation (Montreal), McDonnell-Pew Program in Cognitive Neuroscience, American Parkinson's Disease Association, and a fellowship from Human Frontier Science Program to Jakob Reith.