Decline of Dopamine: Effects of Age and Acute Neuroleptic Challenge

It has been almost 30 years since the methods of nuclear medicine were first applied to the study of psychiatric disorders (1). Early studies examined regional cerebral blood flow and, subsequently, glucose metabolism as measures of neuronal activity (2–5). Soon thereafter, ligands that directly measure the neurobiologic substrates of neurotransmitter function were developed and were used widely in psychiatric neuroimaging (6, 7). The capacity to study neurometabolic and neurochemical activity in vivo relatively noninvasively in patients—and at different stages of their illness and lives—promised to revolutionize psychiatric research and reveal the nature of brain function and disease pathophysiology.

Positron emission tomography (PET) scanning is regarded as the Rolls Royce of neuroimaging. Interest in functional neuroimaging with PET has burgeoned over the years as the relevant technology and methodology with which it is used have become more sophisticated. The reports of Volkow et al. and Bartlett et al. in this issue may be considered in this context.

The study by Volkow and colleagues, in its simple elegance, demonstrates how the power of PET, when applied to a basic question, can yield a potentially profound result. Using PET and the competitive dopamine receptor antagonist [^{11}C]-raclopride as the ligand for quantitative neuroreceptor (D_2) imaging, these investigators found decreases in D_2 receptor densities that correlated with increasing age in a group of healthy volunteers. While this finding has been previously reported (8, 9), Volkow et al. also used standard neuropsychological tests. Remarkably, they found a strong correlation between D_2 receptor density and selective measures of motor and cognitive function, a correlation that could not be explained on the basis of age effects. These included motor function measured by the Finger Tapping Test, abstract thinking and mental flexibility measured by the Wisconsin Card Sorting Test, and attention and response inhibition measured by the Stroop Color-Word Test interference score.

At first glance, it might appear that there is nothing new or noteworthy in these findings. However, this linear association between the measures of neuropsychological function and D_2 receptors is in fact striking, because it was demonstrated in healthy volunteers, not symptomatic patients with neurologic disorders. These results run counter to the dogma derived largely from the literature on Parkinson's disease, in which it has been suggested that an 80% or greater loss of nigrostriatal dopamine function had to occur before clinical manifestations of functional impairment would be evident (10). It has been generally assumed that with lesser deficits, the redundancy in striatal dopamine innervation, and/or various compensatory mechanisms, would obviate the appearance of clinical signs or symptoms. Thus, the report by Volkow et al. of a linear association between decline in aspects of neuropsychological function and decrements in D_2 receptors in healthy volunteers is noteworthy. Their data indicate that the resolution of PET-quantified D_2 binding is sensitive enough to detect functional decrements that are subclinical and asymptomatic and also is sufficient to detect the actual linear relationship between

dopamine neurotransmission (as reflected by D_2 density) and specific motor and cognitive functions as well as age.

Historically, the focus of studies of dopamine and behavior has been on the D_2 receptor, yet recent work has emphasized the role of D_1 receptors in mediating the deficits of aging and disease (11, 12). Work by Goldman-Rakic and co-workers (e.g., reference 13) has demonstrated the role of D_1 receptors in frontal lobe cognitive functions involving working memory. In addition, it has been clearly demonstrated that D_1 agonists can reverse the deficits in motor and neurocognitive function associated with Parkinson's disease and MPTP-induced damage (14–17). Such data not only highlight the important role for D_1 receptors in normal function and non-pathologic aging, but raise interesting questions about possible changes in D_1 receptors that might be revealed in the Volkow et al. paradigm.

The findings of the study by Volkow et al. also illustrate the functional consequences of brain dopamine activity. The Finger Tapping Test is the only measure for which the anatomic basis is predominantly attributable to the corpus striatum of the basal ganglia. The card sorting and Stroop tests are believed to be subserved by cognitive functions that are primarily based in the cerebral cortex. This has two important implications. First, it reaffirms the often reported but less frequently acknowledged fact that the corpus striatum, by virtue of its topographically organized and distributed projections, modulates a wide range of cognitive and motor functions (18). Second, these results demonstrate the distributed anatomic network in which dopamine plays an important functional role (19, 20).

The report of the late Elsa Bartlett and her colleagues is less easy to interpret. Its results are somewhat counterintuitive and not wholly consistent with previously reported studies, though nonetheless interesting. The New York University-Brookhaven PET group had previously shown, as had others, that chronic treatment with antipsychotic drugs decreased glucose metabolic activity in extrastriatal (predominantly cerebral cortical) regions while increasing it in the striatum (21–26). Moreover, it had also been shown that neither D_2 receptor densities nor affinities differed between patients who were responsive and those who were not responsive to antipsychotic drug treatment (27–29), although densities did correlate with plasma drug levels (27, 30). Since the onset of D_2 receptor blockade is rapid (within hours of drug administration) yet therapeutic effects take weeks to occur, Bartlett et al. (21) hypothesized that the critical mechanisms mediating antipsychotic drug effects must be downstream from the receptor and might be reflected by neurometabolic activity. They tested this by measuring glucose metabolic activity not as basal levels under resting conditions or after repeated antipsychotic drug treatment but with a dynamic test 12 hours after parenteral administration of haloperidol (5 mg i.m.). They found that following drug challenge glucose metabolic activity was decreased in all brain regions including the striatum. Moreover, the decrements were greatest in the healthy volunteers and patients classified as treatment *nonresponders.* It is interesting that the responders to treatment showed only minimal change.

These results are puzzling for two reasons. First, the effects of haloperidol on glucose metabolic activity were widespread (essentially in all brain regions measured) and greatly exceeded the known distribution of D_2 receptors. Presumably, this reflects the transduction of D_2-mediated effects across the distributed striatal-thalamic-cortical circuits through which striatal neurons project (18). Second, the direction of the changes in glucose metabolic activity is unusual—haloperidol produced decreased activity, including in the striatum, *except* in treatment-responsive schizophrenic patients. How are we to understand this? Some prior studies indicate that repeated antipsychotic drug treatment increases striatal metabolic activity and decreases cerebral cortical metabolic activity, while others have found increases in cerebral perfusion with drug treatment (22–25, 31). It is notable that brain metabolic studies using 2-deoxyglucose in rodents have shown that acute antipsychotic drug administration generally depresses metabolic activity (32, 33). Although it is possible

that acute single-dose administration produces a different pattern of effects on brain glucose utilization than repeated dosing (34), these disparate findings are not readily reconcilable.

The fact that the greatest changes were seen in the nonresponding patients and normal subjects is also puzzling. Buchsbaum et al. (22, 23) previously reported that low basal levels and greater increases in glucose metabolic activity after repeated antipsychotic drug treatment were associated with better response. Critical data missing from the Bartlett et al. study are the baseline levels of the healthy subjects. Without these values, it is difficult to conclude whether the greater decreases in glucose activity that occurred in the nonresponders were to levels commensurate with those of the normal subjects (i.e., the treatment normalized their aberrant levels). Wolkin et al. (35) reported blunted prefrontal decreases and relative striatal increases in glucose metabolism in response to chronic haloperidol administration in patients with prominent negative symptoms. Poor response to antipsychotic treatment is characteristic of this subgroup of patients (36–38). The Brookhaven group also previously reported that amphetamine challenge decreased cerebral cortical glucose metabolism but that this effect was also blunted in the patients with negative symptoms (39). These results from the same group suggest that the smallest change would be in the patients who were not responsive to treatment—that the treatment-responsive patients would exhibit the greater plasticity and capacity for antipsychotic response (40).

In general, selective or nonselective dopamine agonists produce decreases in cortical glucose metabolism (33, 41–43), although Volkow et al. (44) subsequently found, using methylphenidate, that brain metabolic changes varied by region, possibly because of differences in D_2 receptor availability and/or function. Preclinical studies have shown that this effect is reversed in animals with pharmacological or surgical lesions of the striatum or prefrontal cortex (45). A recent study by Weinberger's group (manuscript by R. Saunders et al. submitted for publication) may help to bring these apparently inconsistent findings into a cogent context. They examined the dopamine response in the caudate nuclei, following pharmacological stimulation with amphetamine of the dorsolateral prefrontal cortex, in adult rhesus monkeys that had had either neonatal or adult lesions of the medial temporal lobe and in normal animals. The normal animals, as well as those with lesions of the dorsolateral prefrontal cortex that were made when they were adults, showed a reduction in dopamine overflow. In contrast, the monkeys with dorsolateral prefrontal cortex lesions made during neonatal periods became hyperdopaminergic (i.e., had decreased dopamine overflow). These data illustrate that early injury to the primate medial temporal lobe predisposes an adult brain to respond to prefrontal cortical stimulation with abnormal striatal dopamine release. Consequently, it could be that pathologies of different types or timing in the course of development result in distinct patterns of neural organization in the striatal-thalamic-cortical architecture that produce varying responses to dopaminergic stimulation.

There is a sense of satisfaction in having an article definitively settle a question in such a way that further research would be only confirmational. However, these two very interesting reports raise as many issues as they settle, and it is clear that further research on these important questions is necessary.

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JEFFREY A. LIEBERMAN, M.D.
RICHARD MAILMAN, PH.D.