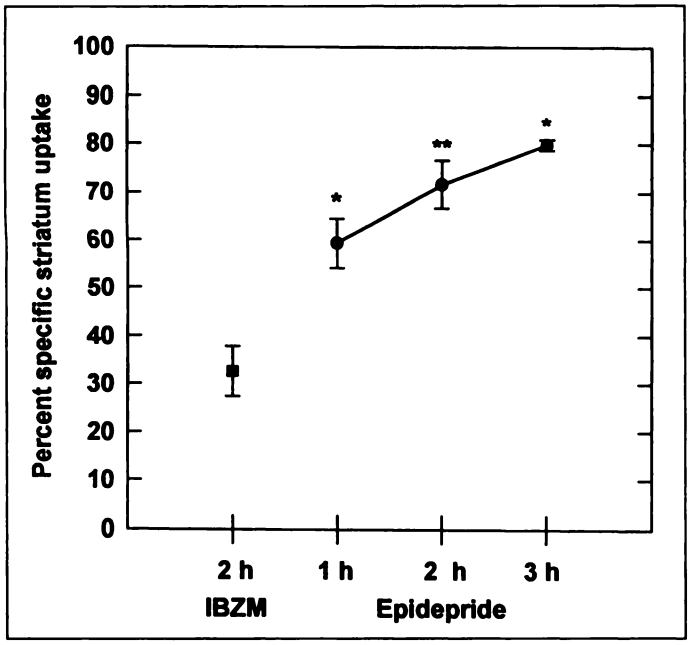

FIGURE 3. Percent specific striatum uptake for ^{123}I-epidepride compared with ^{123}I-IBZM (mean ± s.d.). * $p < 0.05$ compared with ^{123}I-IBZM, ** $p < 0.01$ compared with ^{123}I-IBZM.

the striatum (16.5 pmole/g tissue) are many times greater than those of the thalamus (0.72–1.0 pmole/g), hypothalamus (1.8 pmol/g), pituitary (1.3 pmole/g) and temporal cortex (0.31–0.46 pmole/g) (*19*). Our in vivo results are consistent with this distribution of receptors but, in contrast to the high affinity striatal accumulation of ^{123}I-epidepride, we found only low levels of specific uptake in the extrastriatal sites. Our failure to visualize receptor uptake in the hypothalamus and pituitary probably relates to the smaller volumes of these structures.

It is important to stress that a favorable target-to-background ratio is not sufficient to establish the imaging utility of a radiotracer. Factors related to the radiopharmaceutical itself (ease of preparation, radiopharmaceutical purity, availability and cost), ligand-receptor interaction (reversibility, specificity), in vivo localization (rate of blood clearance, blood-brain barrier permeability, ligand metabolism) and clinical application (characterizing receptor number, receptor affinity or endogenous displacement) also affect radiopharmaceutical choice (*8,20*).

In summary, ^{123}I-epidepride gives high-quality images of the striatum consistent with its known enhanced in vitro receptor affinity.

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EDITORIAL

SPECT Imaging of Dopamine Receptors

PET has become an established method for the in vivo study of neurotransmitter systems. It provides not only unique information of potential clinical significance in several important neuropsychiatric disorders, but it also allows investigation of drug actions in the living human brain. Imaging of some neurotransmitter systems, particularly the dopaminergic and benzodiazepine systems, has also become feasible using SPECT due to the recent development of iodinated neuroligands and advancements in SPECT technology. Both the widespread availability and the lower operating costs of SPECT compared with PET suggest that SPECT imaging of neurotransmitter systems may become an important clinical tool.

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In this issue of *The Journal of Nuclear Medicine*, Leslie et al. (*1*) compare [^{123}I]iodobenzamide (IBZM) and a new neuroligand ^{123}I-epidepride for SPECT imaging of dopamine D2 receptors. They show that ^{123}I-epidepride provides higher quality images of the striatum with enhanced target-to-background ratios compared with IBZM. The work of Leslie et al. and related work on ^{123}I-epidepride reported elsewhere (*2*) represent an important effort to improve SPECT imaging of neuroreceptors. Considering the limitation of SPECT in terms of spatial resolution and detector sensitivity compared with PET, the high target-to-background ratio provided by ^{123}I-epidepride is a desirable imaging characteristic. As suggested by Leslie et al. (*1*), however, several other important features of the neuroreceptor ligand need to be considered in order to extract information on receptor binding from image data on a scientifically sound basis. Also critical to the application of this technique to clinical studies is the need for simple and readily accessible methods to obtain such information. In anticipation of the clinical utilization of this technique in the near future we discuss several pertinent features of SPECT imaging of dopamine receptors, including dopamine receptor physiology, potential clinical applications, neuroligand selection and image data analysis.

DOPAMINE RECEPTOR PHYSIOLOGY

Currently, both pre and postsynaptic phases of dopaminergic transmission can be imaged with SPECT. Imaging of dopamine re-uptake sites (transporters) located on the presynaptic nerve terminals in the striatum using a cocaine analog ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT) is a potent method to assess the integrity of presynaptic dopaminergic neurons (*3*).

In contrast, imaging of postsynaptic dopamine receptors is complicated by the existence of several receptor subtypes. Originally, only two types of brain dopamine receptors, D1 and D2, were known (*4*). These receptors can be differentiated pharmacologically using D1 and D2 receptor-selective agonists and antagonists. The recognition that dopamine receptors, however, belong to a family of G-protein coupled receptors resulted in a discovery of the molecular diversity of dopamine receptors (*5*). Hence, dopamine receptors currently include D1 through D5 receptors that fall into two classes: D1-like receptors (D1 and D5) and D2-like receptors (D2, D3 and D4). The D1-like receptors interact with G_s complexes resulting in the activation of adenylate cyclase, whereas D2-like receptors interact with G_i complexes to inhibit this enzyme. D3, D4 and D5 types are one to two orders of magnitude lower in abundance than D1 or D2 types (*6,7*). D1 and D2 receptors are found mostly in the striatum but D3 and D4 receptors are more selectively associated with the limbic brain (*8*).

Over 80% of brain dopamine is found in the striatum and the nigrostriatal dopaminergic pathway is an essential part of the basal ganglia-thalamocortical circuits. These circuits include motor, prefrontal and limbic systems (*9*). The latter two are largely associated with cognitive and emotional functions. Recent evidence suggests that dopamine differentially regulates the two parallel output pathways from the striatum which exert opposing effects upon the thalamus. These include the direct pathway via D1 receptors and the indirect pathway via D2 receptors (*9–12*).

A selective loss of D2 receptor neurons in the striatum in the early stage of Huntington's disease, for example, is thought to result in the development of spontaneous movement (chorea) by releasing thalamic inhibition via the indirect pathway (*12*). The additional loss of D1 receptor neurons in the later stage of this disease results in the development of bradykinesia and akinesia by increasing thalamic inhibition via the direct pathway (*13*).

Traditional neuroleptics selectively block D2 receptors. The antipsychotic effects of these neuroleptics are probably related to the D2 receptor blockade in the nonmotor circuits whereas the D2 blockade in the motor circuit prevents dopamine from inhibiting the indirect pathway and may result in the unwanted development of hypokinesia by increasing thalamic inhibition.

Although neuroligands for imaging D1 and D2 receptors have been developed, most of the studies to date have focused on D2 receptor imaging. IBZM is the first neuroligand developed for SPECT imaging of D2 receptors. Newly developed iodinated D2 receptor ligands include ^{123}I-iodobenzofuran (IBF), ^{123}I-epidepride, ^{123}I-lisuride, ^{123}I-2′-iodospiperone and ^{123}I-NCQ 298. Both IBZM and IBF are known to also have significantly high affinity for D3 receptors, but negligible affinity for D4 receptors (*14,15*). To date, no neuroligands are available to selectively image D3 or D4 receptors.

POTENTIAL CLINICAL APPLICATIONS

The dopaminergic system is implicated in the pathogenesis of several neuropsychiatric illnesses including movement disorders, schizophrenia and mood disorders as well as certain neuroendocrine diseases. The potential clinical utility of SPECT imaging of D2 receptors in various movement disorders including Parkinson's disease, Huntington's disease, progressive supranuclear palsy, multiple system atrophy and Wilson's disease have been recently evaluated (*16–20*). These studies generally have demonstrated decreased D2 receptor binding in these conditions except for Parkinson's disease where the postsynaptic dopaminergic system is usually intact. Thus, D2 receptor SPECT imaging is a promising tool in the diagnosis/differential diagnosis of these extrapyramidal diseases and may be used to predict treatment response to dopaminergic therapy (*19*). Additionally, β-CIT SPECT will play an important complementary role in disorders such as Parkinson's disease which is characterized by degeneration of presynaptic nigrostriatal dopaminergic neurons (*21*).

Another potential use of dopamine receptor SPECT may be in monitoring antipsychotic therapy with neuroleptic agents. The practice of treating psychotic symptoms with neuroleptics has been accepted since the mid-1950s, but there is no well-established practical method to predict individual response to treatment. These therapies may produce extrapyramidal side effects. Neuroleptics are considered to produce extrapyramidal effects by blockade of central dopamine D2 receptors. The antipsychotic potency of neuroleptics generally correlates linearly with their affinity for D2 receptors (*22*). Although previous SPECT and PET studies suggest the possible existence of somewhat complex relationships between the antipsychotic effect and the degree of D2-receptor blockade (*23–26*), the production of extrapyramidal side effects is generally associated with high D2-occupancy by traditional neuroleptics (*27,28*). Recent evidence suggests that atypical neuroleptics which selectively block other D2-like receptor subtypes, including D3 and D4, may produce enhanced antipsychotic but reduced extrapyramidal side effects (*29*). Further studies will be needed to establish the potential role of dopamine receptor imaging in neuroleptic therapy.

SPECT imaging of D2 receptors has shown alterations in the striatal D2 receptor distribution and binding in some schizophrenic patients before antipsychotic therapy (*30*) although the clinical implication of these finding sare not clear at the moment. In addition, the dopami-

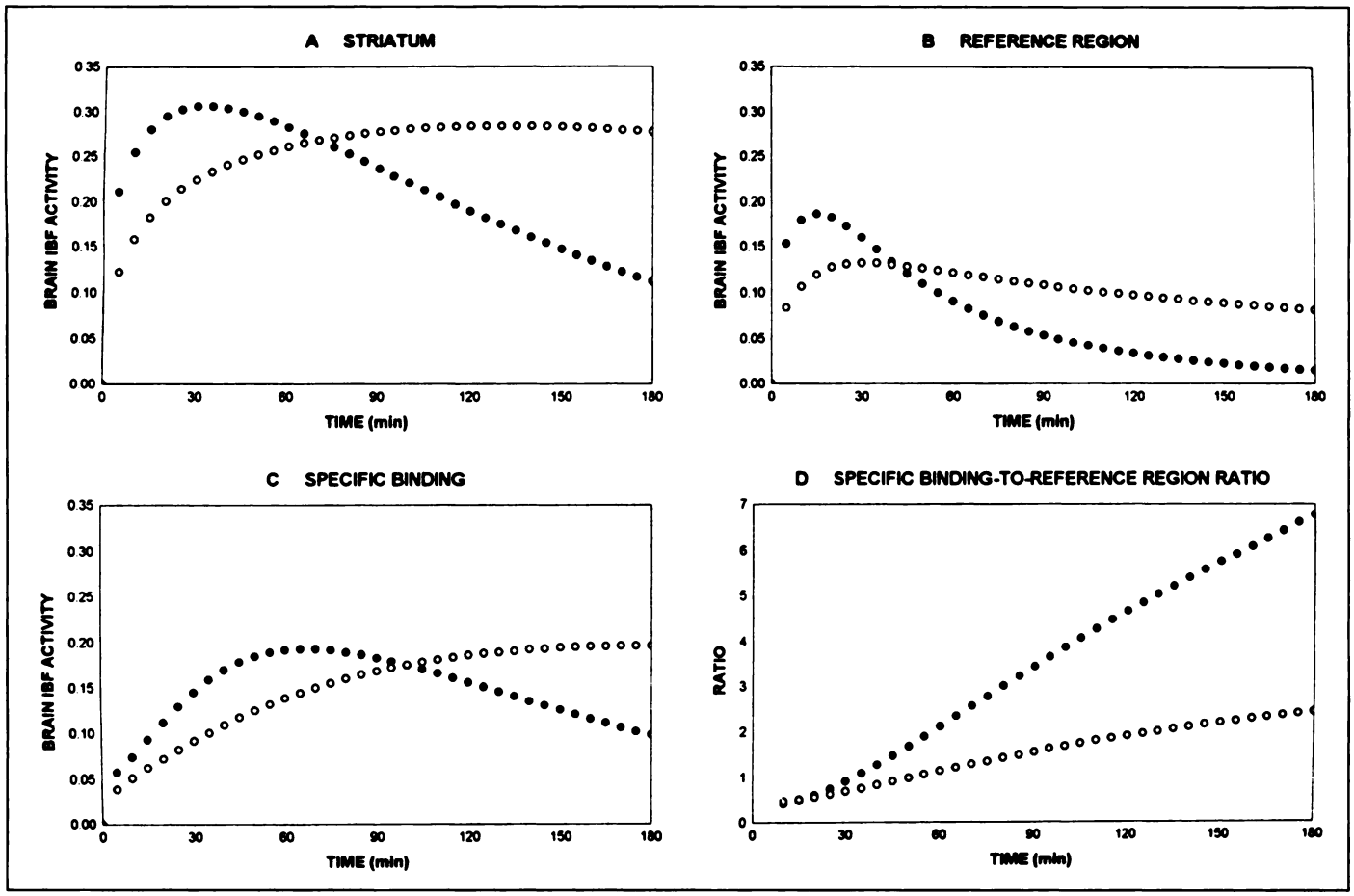

FIGURE 1. Plots of regional brain time IBF activity in the striatum (A), reference region (B), specific binding (striatum minus reference region) (C) and specific binding-to-reference region ratios (D), respectively, of two hypothetical subjects after a bolus injection of IBF. These plots have been created based on a three-compartmental model using identical values of receptor parameters (B_{max}/K_D and k_3/k_4) but using combinations of differing parameter values for rCBF and peripheral ligand clearance, selected from the previously reported data (*32*). These plots illustrate the dynamic interplay of the receptor density, ligand delivery or rCBF, and clearance. The first subject has high rCBF and fast clearance (●) whereas the second subject has low rCBF and slow clearance (○). In the first subject, the regional activity shows a slightly higher peak uptake occurring at a significantly earlier time compared with the second subject (A,B,C). The specific binding-to-reference region ratio of the first subject is larger than that of the second subject and this difference increases with time (D). To extract correct information on the receptor parameters from image data, therefore, measurements made at a single arbitrary point in time after a bolus injection may not be sufficient.

nergic system along with adrenergic and serotonergic systems may be involved in the pathogenesis of mood disorders. There is evidence to suggest that there may be a subgroup of mood disorders in which the dopamine neuroregulation is altered (*31*). We know of no reported imaging studies of the dopaminergic system that assess its potential role in mood disorders, but future research in these common disorders may prove rewarding.

Finally, certain prolactin and growth hormone producing pituitary tumors are known to be associated with D2 receptors. Characterization of the degree of D2 receptor binding may provide useful information that can be used to decide the specific treatment regimen (*32*). Although a preliminary SPECT study of pituitary adenomas using IBZM did not show encouraging results (*33*), use of a high affinity ligand such as ^{123}I-epidepride and a high spatial resolution SPECT camera may be needed for this kind of study.

NEUROLIGAND SELECTION

Information of interest extracted from imaging studies of neuroreceptors is the receptor density and/or the way in which agonists or antagonists interact with the ligand-receptor binding. The success in accomplishing this goal is influenced by several conflicting properties of the neuroligands used. These include affinity, selectivity, reversibility, lipophilicity and metabolism. A high affinity, low lipophilicity ligand such as ^{123}I-epidepride (K_D = 0.02 n*M* and log k_w = 2.05) generally provides high target-to-background ratios and hence high image quality. For receptor quantification, however, reversibility is needed (*34*). In vivo binding reversibility is promoted by lower affinity and higher lipophilicity. Lower affinity is also important to show the effect of the competitive binding by the agonist or antagonist. Protein binding and nonspecific binding on the other hand increase as lipophilicity increases. For example, IBZM (K_D = 0.41 n*M* and log k_w = 2.75) is a highly reversible ligand with moderate affinity, providing only modest target-to-background ratios. IBF (K_D = 0.09 n*M* and log k_w = 2.32) is positioned between ^{123}I-epidepride and IBZM in terms of affinity and lipophilicity.

For reversibly binding neuroligands such as IBZM, IBF and ^{123}I-epidepride, the time course of regional brain tracer uptake after a bolus ligand injection is determined by the dynamic interplay of the receptor density, ligand delivery or regional cerebral blood flow (rCBF) and peripheral ligand clearance. The latter two factors are not primarily related to the receptors. This interplay is illustrated in Figure 1 which shows regional brain time IBF activity curves and specific binding-to-reference region ratios of two hypothetical subjects with identical receptor parameter values but differing parameter values of rCBF and peripheral ligand clearance. These two different time curves are intended to illustrate that measurements made with SPECT at a

single arbitrary point in time after a bolus neuroligand injection may not provide correct information on the receptor parameter. Thus, proper imaging and data analysis techniques on a scientifically sound basis are required to obtain correct information on the ligand-receptor binding.

IMAGE DATA ANALYSIS

In in vivo receptor quantification, tracer doses of neuroligands are used to measure binding potential, BP = B_{max}/K_D, or k_3/k_4 (the ratio of the transfer constants between the intracerebral nondisplaceable compartment and specifically bound receptor compartment) which is equivalent to BP/V_2, where V_2 is the neuroligand distribution volume in the nondisplaceable compartment. Although it is feasible to measure both B_{max} (receptor density) and K_D (a dissociation constant) separately with SPECT (*35*), these measurements would require usually a second experiment involving very high concentrations of cold ligands at the receptor site. Therefore, this approach would not only be impractical for routine use but also it would be inappropriate for human studies because of the potentially undesirable pharmacological effects.

To date, several different techniques have been developed for in vivo receptor quantification using SPECT or PET. These techniques use either a single bolus injection or a bolus plus constant infusion paradigm. Using IBF given as a bolus and SPECT, Laruelle et al. (*36*) successfully employed kinetic or graphical data analysis techniques to measure B_{max}/K_D in healthy subjects. This approach, however, would not be appropriate for routine clinical settings because it not only requires repeated arterial blood sampling, but it is also technically demanding, requiring metabolite analysis and accurate cross-calibration between plasma and tissue radioactivity measurements. A solution to avoiding arterial blood sampling might be to use a standardized arterial input function based on a normative sample (*37*). This approach would be reasonable for certain neuroligands which show a small intersubject variability in both peripheral metabolism and clearance.

Alternatively, k_3/k_4 may be measured based on the bolus injection paradigm and a graphical approach using a tissue reference region instead of an arterial input function (*15*). Advantages of this approach are: (a) elimination of invasive arterial blood sampling; (b) measurements are not influenced by rCBF or peripheral clearance; and (c) measurements are free of errors of plasma measurements including errors of metabolite corrections as well as errors of cross-calibration between plasma and tissue measurements. Thus, this approach may be applicable to clinical situations. The practical significance of this measure which incorporates V_2 in addition to BP needs to be evaluated in various disease conditions.

SPECT is generally at a disadvantage compared with PET in terms of spatial resolution and detector sensitivity. In receptor quantification, however, the long physical half-life of ^{123}I can offset these disadvantages, and it can even provide imaging opportunities of clinical significance that are not feasible with short-lived PET tracers (*38*). Iodine-123-epidepride with high affinity and low lipophilicity, for example, provides excellent image quality with high target-to background ratios. Its low reversibility should allow adequate sampling time with SPECT to characterize the in vivo pharmacokinetic behavior required for receptor quantification. It would, however, probably take several hours of scanning to accomplish this task. The prolonged scan sessions are not practical, adding to the patient discomfort and increasing the chance of head motions. IBF in this respect may provide a reasonable trade off between the conflicting requirements of reversibility and target-to-background ratios, allowing imaging to be complete within a shorter time period post bolus injection.

β-CIT with very low reversibility, on the other hand, allows measurements of k_3/k_4 from one short scan during 18–24 hr postbolus injection because it establishes protracted equilibrium (*3*). For BP measurements, only one venous sample is required. This approach is made feasible by the 13-hr half-life of ^{123}I. The half-life of ^{123}I is actually long enough to allow commercial supply which is not possible with PET agents. In addition, progress toward the development of ^{99m}Tc-labeled agents promises to make receptor imaging with SPECT even more widely available (*39,40*).

The paradigm involving bolus plus constant infusion of reversibly binding neuroligands simplifies receptor quantification greatly by creating sustained equilibrium (*35,41*), similar to the protracted equilibrium with β-CIT after bolus injection. Practically speaking, this paradigm is better suited for SPECT than PET because of long-lived ^{123}I, although it has been successfully used with PET, in animals (*42*). Additionally, this paradigm can be a powerful research tool not only to study dynamic changes in the receptor ligand binding after administration of competitive agonists or antagonists but also to measure changes in endogenous dopamine levels after pharmacological challenge (*14*). Thus, it is feasible to measure not only dopamine receptors but also dopamine itself with SPECT. To show these changes effectively and to achieve equilibrium within a reasonable time period, however, this paradigm would require neuroligands with relatively low affinity and high reversibility. For this reason, IBZM has been used at the expense of low target-to-background ratios (*14*). Even with IBZM, however, it takes at least 3 hr of constant infusion to achieve sustained equilibrium and the practicality of this paradigm as a potential clinical tool needs to be evaluated.

Finally, further advances in SPECT technology are desired to make proper correction methods for attenuation and scatter available for routine use. This improvement should allow interinstitutional as well as intersubject comparisons of SPECT measures of receptor parameters more accurately.

CONCLUSION

With the recent development of several iodinated neuroligands and advances in imaging technology, SPECT imaging of dopamine receptors is a reality with potentially useful clinical applications in several important neuropsychiatric disorders. The ultimate clinical utility of this technique of course will depend on whether it can affect patient outcome in a cost-effective way.

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Brain SPECT with Dipyridamole Stress to Evaluate Cerebral Blood Flow Reserve in Carotid Artery Disease

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This is a preliminary study of SPECT brain scan using dipyridamole as a stress agent to assess cerebral blood flow reserve in six patients with severe carotid artery disease. **Methods:** We performed SPECT scanning of the brain, with and without dipyridamole stress. Dipyridamole (0.57 mg/kg) was given intravenously 3 min before infusion of ^{99m}Tc-HMPAO. Patients were studied 30 min later using a rotating head gamma camera. The scans were analyzed qualitatively and semiquantitatively. An acetazolamide stress SPECT image was also obtained in two patients. **Results:** All patients had at least 80% stenosis in one internal carotid artery, three of them also had contralateral carotid stenosis. The dipyridamole SPECT showed an increased region of hypoperfusion in the hemisphere ipsilateral to the severe carotid disease in four patients. That suggests poor perfusion reserve and the potential risk of regional ischemia. In four of six patients, side-to-side asymmetry increased from the baseline condition after injection of dipyridamole. The asymmetry index increased more after dipyridamole than after acetazolamide injection in two patients. **Conclusion:** This study suggests that dipyridamole stress SPECT is useful in assessing cerebral blood flow reserve. It demonstrates the region of poor vascular reserve in patients with severe carotid artery disease. Dipyridamole SPECT scans show more extensive hypoperfusion than acetazolamide in the two cases.

Key Words: SPECT; brain; dipyridamole; acetazolamide

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