Somatostatin Receptors in Schwannomas

TO THE EDITOR: In a recent letter to the Editor, van Steelandt et al. (*1*) reported that they were able to detect somatostatin receptors in schwannomas using an indirect in vitro technique based on the immunohistochemical detection of exogenously applied somatostatin which bound to the somatostatin receptors searched for. The idea to use such an indirect technique to identify receptors is not new. It is appealing in this case since it requires only a somatostatin antibody rather than a somatostatin receptor antibody (not commercially available). Moreover, this method does not rely on the cumbersome method of binding of radiolabeled somatostatin analogs, as they are used for example in receptor autoradiography (*2*). It is theoretically easy to conceive that a tissue section can be preincubated with unlabeled somatostatin, which will then bind to specific somatostatin receptors located in that tissue and which, after washing the unbound somatostatin, will remain bound to the receptor and be detected with the immunohistochemical method using somatostatin antibodies. However, the development of the idea towards a practicable and accurate method of receptor measurement has never been completed, due to a number of problems that are difficult to solve.

With such a method, the following critical points, which are not restricted to somatostatin receptors only, have to be considered:

1. An optimal incubation condition has to be found in order to permit the ligand to bind specifically and to bind irreversibly (cross-link) to the specific receptor. The proof that a co-valent ligand-receptor binding has occurred is essential.
2. The proof of the very high affinity and saturability of the receptor under investigation has to be given. In this respect, it should be mentioned that the concentration of the ligand in the incubation solution should be kept low and chosen in relation to the K_D value of the respective receptor (nanomolar concentration rather than micromolar concentration).
3. The washing steps, in which unbound ligand has to be washed out from the section, have to be well controlled to make sure that no free ligand remains in the tissue. Free ligand might be either the exogenously applied ligand or endogenous peptide; both could be recognized by the antibody and give a false-positive result.
4. One has to make sure that the antibody, which normally recognizes the ligand when it is free in solution, also will be able to recognize the ligand once it has bound to its receptor (the ligand, bound within receptor pockets, may not be reached and/or recognized by the antibody in that location).
5. It also is essential to control the method by using adequate negative tissue controls, i.e., tissues that do not contain somatostatin receptors to exclude the generation of false-positive results by incompletely washed-out somatostatin. Of course, the evaluation of the results obtained with this immunohistochemical method should be performed in parallel with other, established methodologies like, for instance, in vitro receptor autoradiography, as mentioned by van Steelandt et al. (*1*).

Therefore, although the indirect immunohistochemical methodology described by van Steelandt et al. (*1*) may be economical and easy to perform, it is not yet sufficiently clear whether it is adequate to identify somatostatin receptors. In the 11 Schwannomas recently analyzed for somatostatin receptors using receptor autoradiography, we were unable to identify significant amounts of somatostatin receptors (*3*). For the time being, and until a fully controlled indirect immunohistochemical method is reported, it is probably safer to rely on established binding methods like receptor autoradiography or to wait until an adequate somatostatin receptor antibody is available for direct immunohistochemical staining of these receptors.

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Jean Claude Reubi
Institute of Pathology
University of Berne
Berne, Switzerland

Captopril Renography in the Detection of RVH

TO THE EDITOR: In a recent article in *The Journal of Nuclear Medicine*, Schreij et al. (*1*) recommended against performing captopril renography to detect renovascular hypertension in patients with a high clinical suspicion of disease because they claimed that their captopril renography data showed poor sensitivity in comparison to the angiographic diagnoses. This is in contradiction to the sensitivity data reported in the literature (*2–4*) and also in contradiction to the conclusion drawn in the following publication of Blaufox et al. (*4*) who pointed out that captopril renography appears to be the most cost-effective investigation for diagnosis of renal vascular hypertension in a patient group with a disease prevalence of 30% since it obviates the need of an arteriogram in many patients.

There are several obvious objections to the conclusions Schreij et al. (*1*) drew from their data. The most important objection concerns the fact that angiography alone cannot be used as the gold standard; the gold standard should be the outcome after revascularization. Angiographically stenosed renal arteries may not be hemodynamically responsible for the development of hypertension and thus an eventual revascularization may not lead to an improvement or cure. Thus, so called false-negative studies may instead be true-negatives changing the reported sensitivity and specificity. It would also be important to know the training and experience of the physicians interpreting the studies. For example, were they familiar with pitfalls such as the influence of urine flow, the influence of medication, the influence of time after ingestion of the drug, the influence of a meal before the test, the use of cortical versus total kidney renograms, the use of plasma renin response to captopril, etc. Such information is lacking in the publication and should be discussed. It is particularly important that the reader of *The Journal of Nuclear Medicine* does not take Schreij et al.'s (*1*) publication as representative since there is overwhelming evidence that the sensitivity of captopril renography studies is high and that such studies should be preferred from a cost-benefit standpoint view in patients suspected to have renal artery stenosis (*4*). Without giving or discussing the reason of the unexpected low sensitivity of the captopril renography studies a report of such low performance of nuclear medicine physicians is hardly worth to be published.

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Roland Muller-Suur
Karolinska Institute
Danderyd, Sweden

REPLY: We thank Dr. Müller-Suur for his interest in our article. We reported the intra- and interobserver agreement between experienced nuclear medicine physicians who evaluated renograms. The agreement was found to be reasonably good, but the sensitivity and post-test probability of their renographic diagnosis in relation to the angiographic diagnosis was rather poor (*1*).

Numerous reports have documented a sensitivity and specificity ranging from 41% to 100% (*2*). However, almost all of these studies were performed retrospectively and all of them excluded patients with a "negative" renogram from undergoing renal angiography. Consequently, we have never been informed about the true false-negative rate of renography. Moreover, several investigators did not define the degree of stenosis that was considered to be significant. For these reasons, we think that most of these studies do show better results than ours, even though some also report a low sensitivity (*2*).

We also agree that renal angiography only determines the degree of stenosis and does not foretell whether a stenosis is hemodynamically responsible for the development of hypertension. A diagnosis of a hemodynamically important stenosis (causing hypertension), however, can only be made retrospectively, i.e., after correction of the stenosis. Since the renographic criteria of a hemodynamically important stenosis have not been formulated unequivocally and since no clinician will refrain from ordering a renal angiogram in a patient with a positive renogram, the concept of a hemodynamically important stenosis has no practical consequences for the screening of patients suspected of having renal artery stenosis. Furthermore, when an intervention fails to lower the blood pressure, this does not confirm renovascular hypertension, but does not exclude this diagnosis either.

All three readers who participated in our study are skilled nuclear medicine physicians with many years of academic practice experience, and they are familiar with the pitfalls of renogram interpretation. All the patients in the study had renograms performed in the morning after an overnight fast. Voiding of at least 1 cc/min during the investigations was also ensured. Antihypertensive drugs were discontinued at least 3 wk before the tests (which, incidentally, was not always done in other studies).

Our experiences with the plasma renin response to captopril in 49 patients have been published elsewhere (*3*). The baseline and captopril renograms of the first 28 patients in that series were used in our study. The receiver-operator characteristic curves of both baseline and postcaptopril peripheral renin levels indicated that renin levels did not discriminate between patients with essential hypertension and patients with renal artery stenosis.

In conclusion, we still feel that the use of (captopril) renography in patients with a strong clinical suspicion of renal artery stenosis is of limited screening value, based on many reports of studies that have not been performed prospectively or that excluded patients with a "negative" renogram from undergoing renal angiography. Therefore, we recommend further research in this area. This research should concentrate on new radiopharmaceutical tracers and on better criteria to define the hemodynamic significance of renal artery stenosis.

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G. Schreij
P.W. de Leeuw
Academisch Ziekenhuis Maastricht
The Netherlands

Discordant Uptake of MIBI and HMPAO

TO THE EDITOR: We read with interest the case report of Shih et al. (*1*) on discordant uptake of ^{99m}Tc-MIBI and ^{99m}Tc-HMPAO uptake of recurrent occipital meningioma on brain SPECT images. We have recently performed a similar study on 20 primary, 15 metastatic and 4 unverified brain tumors, and on 12 patients with recurrent brain tumors. This report was accepted for oral presentation at the forthcoming EANM Congress in Copenhagen in September 1997 (*2*). Increased accumulation of MIBI was found in 7/7 meningiomas, 7/11 gliomas, 2/2 neurilemmomas, 2/4 unverified and 10/15 metastatic tumors (total 41 patients). In the patients with recurrent tumor, we found increased MIBI accumulation in 7/8 recurrent meningiomas and 3/4 recurrent gliomas. Technetium-99m-HMPAO studies were much more discordant (28 patients). Increased accumulation was found in 2/7 meningiomas and decreased activity was found in 4/7. In the glioma subgroup, increased accumulation was found in 3/11 gliomas and decreased activity was found in 2/11. For metastatic tumors, increased activity was found in 2/8 patients and was decreased in 6/8.

Augmentation of the MIBI image was achieved by delayed imaging after 4 hr (3/6 patients) or by repeating the study after intravenous injection of aminophylline (4/6 patients). These results indicate some usefulness of ^{99m}Tc-MIBI scanning when PET is unavailable, especially in meningiomas and recurrent tumors. As for HMPAO, we agree with Shih et al. (*1*) on the limited value of MIBI/HMPAO scanning in brain tumors—it may be, with the exception of metastatic tumors, where decreased uptake is frequent.

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Piotr Lass
Department of Nuclear Medicine
Medical University
Gdansk, Poland

Evaluating the Significance of Changes in Brain SPECT

TO THE EDITOR: The article by Ito et al. (*1*) presents a potentially valuable addition to the subject of SPECT evaluation of depression. The significance of their results is difficult to evaluate due to apparent conflicts in the description of their statistical methodology.

The article states that a voxel-by-voxel analysis was performed, and that for the bipolar and unipolar groups a Student's t value of 2.10 and 2.16, respectively, was used as their Bonferroni adjusted cutoff points for generating the results images presented.

Unfortunately, this statement does not appear to be supported by their data. Indeed for 18 and 13 degrees of freedom, respectively (based on the number of patients given for the three groups) and an uncorrected value of $p = 0.05$, the statistical table for critical t values (*2*) shows exactly the 2.10 and 2.16 values reported as thresholds. Even a minimal Bonferroni correction would have had to generate a much lower p value:

$$\frac{p}{\text{no. of uncorrelated areas}}, \qquad \text{Eq. 1}$$