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.

REFERENCES

1. van Steelandt H, de Geeter F, van Renterghem D, Michielssen P, Ramael M. Neuropeptide receptor imaging of Schwannoma [Letter]. *J Nucl Med* 1996;37:1272.
2. Reubi JC. Neuropeptide receptors in health and disease: the molecular basis for in vivo imaging. *J Nucl Med* 1995;36:1825–1835.
3. Reubi JC, Waser B, Laissue JA, Gebbers J. Somatostatin and vasoactive intestinal peptide receptors in human mesenchymal tumors: in vitro identification. *Cancer Res* 1996;56:1922–1931.

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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.

REFERENCES

1. Schreij G, van Kroonenburgh MJ, Heidendal GK, van der Pol HA, de Leeuw PW. Interpretation of a captopril renography by nuclear medicine physicians. *J Nucl Med* 1995;36:2192–2195.
2. Prigent A. *Eur J Nucl Med* 1993;20:625–644.
3. Taylor A, Nally. *AJR* 1995;164:31–41.