False Adrenergic Transmitters and Positron Emission Tomographic Imaging of Myocardial Sympathetic Innervation

Irwin J. Kopin, MD

During the past 50 years, isotopic tracer methods have become standard techniques for analysis of dynamic biochemical and physiological processes in vitro and in vivo. When liquid scintillation spectrometry was introduced approximately 35 years ago, assay of β emitting isotopes was simplified. This resulted in widespread application of isotopic methods to study metabolism and disposition of physiologically important substances and drugs. The development of autoradiography made possible direct quantitative imaging of radioisotopically labeled compounds in tissue. With the advent of computer-assisted tomographic methods, it became possible to image quantitatively, in intact animals and in humans, isotopes that emit high-energy, penetrating radiations. The spatial resolution that can be obtained when imaging positron-emitting isotopes (e.g., carbon-11, oxygen-15, nitrogen-13, and fluorine-18) is superior to other types of radioisotopes. Problems of production and rapid incorporation of these relatively short-lived positron-emitting isotopes into appropriately selected radiopharmaceuticals are being solved, and an increasing number of processes are being studied with positron emission tomography (PET). In this issue of Circulation, Schwaiger et al report the use of PET imaging of myocardial radiographic demonstration of administered [3H] norepinephrine in sympathetic nerves in the cat heart.4 The physiological importance of this process is evident from the enhanced sensitivity to administered norepinephrine that occurs after denervation or with pharmacological blockade of uptake. In addition to neuronal uptake (uptake-1), there is also present in heart and other tissues a second uptake system (uptake-2), which becomes apparent at high norepinephrine concentrations; uptake-2 reflects mainly extraneuronal uptake.6 Uptake-1 and neuronal retention of [3H]norepinephrine in the various tissues are dependent on its delivery via the perfusing blood, its diffusion through the tissue to the region of the nerve terminals, and the density of the sympathetic nerve terminals that capture and store the labeled amine.7 Thus, the heart, which is both richly perfused and densely innervated by sympathetic nerves, accumulates norepinephrine from the circulation more rapidly per gram of tissue than any other tissue.7 Other substances that are substrates for uptake-1 would also be expected to be concentrated in the myocardial sympathetic neurons. The observations that [3H]norepinephrine, which is taken up and stored, can be released by nerve stimulation8 and that ganglionic blockade slows release of the labeled amine from the heart9 established the basis for its use as an index of sympathetic neuronal function. Studies of the kinetics of [3H]norepinephrine in tissues of animals have provided a wealth of information about alterations in adrenergic activity during stress, after drug administration, or as a result of induced or genetic disorders. It has not been possible, however, to examine directly in human tissues other than blood the kinetics of uptake and release of norepinephrine. PET imaging of appropriate labeled compounds, however, may provide opportunities to obtain such information.

False adrenergic transmitters and norepinephrine are stored, released, and transported by the same mechanisms.10 Appropriate positron-emitting isotopically labeled false transmitters might then provide a means for quantitative imaging of adrenergic neurons and assessing sympathetic neuronal function.
Metaraminol, one of the first false adrenergic transmitters to be identified, may be a better index of uptake-1 than norepinephrine. Not only is metaraminol resistant to metabolism, but it also differs from norepinephrine in its binding affinities. The affinity of metaraminol and other monophenols for vesicular storage sites is less than that of catecholamines, whereas their affinity for uptake-1 may be more than that of norepinephrine.

Metaraminol labeled with $^{18}$F in the 6-position was shown by Wieland et al to accumulate rapidly in the heart, where it was avidly retained for the duration of the experiment (4 hours). In regionally denervated phenol-treated dog hearts, retention of $^{18}$F was highly correlated with residual endogenous norepinephrine levels. Furthermore, chemical denervation with 6-hydroxydopamine, blockade of uptake-1 with desipramine, or pretreatment with reserpine markedly diminishes the amount of $^{18}$F found in the rat ventricle 90 minutes after injection of $^{18}$F-6-fluorometaraminol. Although good myocardial imaging of $^{18}$F was obtained in dogs, the relatively low specific activity of the labeled compound was thought to require a dose of unlabeled 6-fluorometaraminol that might be unsafe for use in cardiac patients. Use of [$^{11}$C]hydroxyephedrine, the N-methyl analogue of metaraminol, appears to avoid such dangers and is a promising new approach for PET imaging of the neuronal uptake and storage processes. The metabolic stability and avid uptake that enhance the value of metaraminol and its derivatives for assessing uptake-1 may, however, limit their ability to reflect the turnover rate of endogenous norepinephrine. Because of their potential use for PET imaging, the possibility that fluorinated catecholamines are false adrenergic transmitters was investigated. 6-Fluorodopamine is taken up into sympathetic nerve terminals, where it is largely converted to 6-fluoronorepinephrine and retained in the storage vesicles. The fluorinated catecholamines are released during sympathetic nerve stimulation, and the uptake and turnover rates of tritiated and fluorinated norepinephrine in the rat heart appear to be almost identical. Recently, the feasibility of using $^{18}$F fluorodopamine for PET imaging of sympathetic neurons in the heart, spleen, and salivary gland was demonstrated in dogs. Uptake of the fluorine tracer was markedly reduced after sympathetic denervation or after pharmacological blockade of neuronal uptake by administration of desipramine. Unlike the radio-labeled metaraminol derivatives, the level of myocardial $^{18}$F declined significantly during an interval of only a few hours. Furthermore, the rate of decline in radioactivity was slowed by ganglionic blockade and accelerated by infusion of tyramine. Thus, fluorinated catecholamines appear to also hold promise for assessing sympathetic nerve function by PET quantitative imaging.

By examining accumulation rates of metaraminol and amines that are substrates for monoamine oxidase, Carlsson and Walden differeniated the effects of drugs on uptake-1 from effects on vesicular storage. Thus, differences in the metabolism and disposition of the metaraminols and of fluorocatecholamines may provide valuable complementary information about the various processes that support adrenergic neurotransmission and sympathetic neuronal function. However, as indicated by Schwaiger et al, careful validation will be required before effects of drugs or of disorders on false transmitters can be assumed to reflect similar effects on norepinephrine.

References

15. Iversen LL: Inhibition of noradrenaline uptake by drugs. J Pharmacol Exp Ther 1965;145:828–829
18. Eisenhofer G, Hovey-Sion D, Kopin IJ, Mileitch R, Kirk KL, Finn R, Goldstein DS: Neuronal uptake and metabolism...


(Circulation 1990;82:646–648)


False adrenergic transmitters and positron emission tomographic imaging of myocardial sympathetic innervation.
I J Kopin

Circulation. 1990;82:646-648
doi: 10.1161/01.CIR.82.2.646

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/82/2/646.citation