《招待講演》

Radiolabeled Metaiodobenzylguanidine to Display Adrenergic Neuron Distribution and Function in the Heart

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The adrenergic nervous system plays an important role in the adaptation of the normal heart to stress. Diseases may cause disturbances in this system that contribute to the clinical features, particularly by inciting arrhythmias and by not supporting myocardial function in heart failure. When labeled with a radioactive iodine, metaiodobenzylguanidine (MIBG) acts in mammals as an analog of the physiologic adrenergic neurotransmitter, norepinephrine (NE). Evidence for the similarity between MIBG and NE is derived from experiments in animals where adrenergic neuron integrity was disrupted.

Six-hydroxydopamine injures adrenergic neuron terminals and, in the rat heart, the concentration of endogenous NE was reduced to 12% and that of $[^{125}I]$MIBG to 31%. Desipramine, which inhibits the uptake-1 mechanism in adrenergic nerves, caused a reduction in the uptake of $[^{3}H]$NE to 6%, and of $[^{125}I]$MIBG to 50%. The discrepancies between the results with NE and MIBG can be attributed to a larger non-neuronal component for $[^{125}I]$MIBG (up to 20% of the total concentration), and to a dual uptake system which, as shown in cultures of adrenal medulla cells, transports $[^{125}I]$MIBG 1) by a diffusion pathway (which carries little NE) and 2) by the classic uptake-1 pathway (which is the principal route for the uptake of NE).

In dogs, $[^{123}I]$-labeled MIBG is concentrated so that adrenergic neurons of the heart can be displayed by scintigraphy. Phenol applied to the epicardial surface causes injury less than 1 mm in depth but disrupts adrenergic neurons in the region to produce denervation of myocardium beneath the epicardium, and of myocardium on the apex side of the phenol-induced injury. Phenol was painted on the epicardium of dogs' hearts to inscribe rectangles of 3×2 cm and 2×2 cm; consequently, scintigraphic tomographs of the hearts portrayed decreased concentrations of $[^{123}I]$MIBG in regions of myocardium. The regions of diminished concentrations of $[^{123}I]$MIBG corresponded to the denervated sites of phenol application (on either anterior or posterior myocardial walls) and to the denervated myocardium on the apex side of the sites.

Occlusion of coronary arteries produced infarcts that were readily visible as regions of decreased concentration of $[^{201}Tl]$ on scintigraphic tomographs, but, in the same hearts, the regions with decreased $[^{123}I]$MIBG were often larger and therefore indicated peri-infarct denervation. Inducible arrhythmias were more common in the presence of larger infarcts, and possibly these arrhythmias were more frequent when the region of peri-infarct denervation was larger. The dogs were later sacrificed, and, in *ex vivo* assays, the reduced concentrations of radiolabeled MIBG correlated well with the lower levels of endogenous NE in the same segments of myocardium.

The functional activity of adrenergic neurons was decreased in rats by fasting and by the administration of clonidine, an alpha-2 receptor agonist. The decreased function was associated with significantly ($p<.01$) decreased rates of disappearance of $[^{125}I]$MIBG from the heart (but at somewhat more rapid rates than those of $[^{3}H]$NE). The administration of yohimbine, an alpha-2 antagonist, increases the functional activity of neurons, and this change in function was accompanied by significant increases in the rates of disappearance of both [^{125}I]MIBG ($p<.01$) and [^{3}H]NE ($p<.02$) from the heart. Thus, acute changes in neuron function are reflected in the rates of disappearance of [^{125}I]MIBG from the heart.

Based on the animal data, the variations in distribution of [^{123}I]MIBG in the hearts of people can be comprehended. Patients with autonomic neuropathy (two with idiopathic, two with diabetic and one with the central form of Shy-Drager) exhibit diminished concentrations of [^{123}I]MIBG in their hearts three hours after injection, patterns interpreted as indicating loss of adrenergic innervation of the heart. Because the diminution in [^{123}I]MIBG was not uniform, an unbalanced adrenergic stimulation of the heart appeared to exist, and since one of the patients died unexpectedly, this pattern of neuropathy in the heart may predispose to arrhythmias.

Three patients with myocardial infarcts of 23 days or less in duration manifested a generalized decrease in [^{123}I]MIBG concentration in their hearts, but two patients with infarcts of 2 and 15 months duration had only focal decreases of [^{123}I]MIBG in the regions of the infarcts. The infarction may cause a temporary generalized decrease in neuron function but a more permanent loss of neuron function in the infarct and peri-infarct regions.

Patients were tested during desensitization to phobias to evaluate the effects of emotional stress on the disappearance of [^{123}I]MIBG from the heart. In two patients, the rates of disappearance were measured beginning 18 hours after injection of [^{123}I]MIBG, and the desensitization appeared to increase the rate of disappearance. However, in three patients the rates of disappearance were measured beginning 2.5 hours after injection, and desensitization then did not appear to change the rate of disappearance. It may be that at 2.5 hours after injection of [^{123}I]MIBG there is non-neuronal [^{123}I]MIBG limiting the ability to measure precisely rates of disappearance of [^{123}I]MIBG, but that, later on, this non-neuronal component has less influence so that eventually rates of disappearance may accurately reflect neuronal activity.

Summary and Conclusions. 1. The movements of radiolabeled MIBG simulate those of NE so that: altered adrenergic neuron integrity and uptake-1 function are reflected in the concentrations of radiolabeled MIBG in the heart; and altered function of the neurons is reflected in changes in rates of disappearance of radiolabeled MIBG from the heart. 2. Autonomic neuropathy manifests diminished and non-uniform decreases in concentration of [^{123}I]MIBG in the heart. 3. Myocardial infarctions appear to impose generalized decreases in uptake of [^{123}I]MIBG by the neurons of the heart for up to 3 weeks, but subsequently the infarcts are manifest as regional decreases of [^{123}I]MIBG concentrations which appear to be the summation of the loss of neurons in the infarct region and denervation in the peri-infarct region. 4. Acute changes in adrenergic neuron function may be reflected in acute changes in the scintigraphically-detected rates of disappearance of [^{123}I]MIBG from the heart. 5. [^{123}I]MIBG offers a non-invasive means of evaluating the integrity and function of the adrenergic nervous system within the heart, and, in the future, may provide valuable information bearing on arrhythmias and heart failure.