Cardiac Neuronal Imaging at the Edge of Clinical Application

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KEYWORDS

• Autonomic • Imaging • Nuclear • Cardiac • MIBG • HED

Neuronal innervation plays a crucial role in cardiac function. The heart is richly innervated with sympathetic and parasympathetic fibers that work in conjunction with circulating catecholamine mediators, such as norepinephrine (NE), to tightly regulate cardiac output at rest and during periods of increased cardiac demand. An impairment of cardiac autonomic function, most often the result of cardiac disease (although sometimes secondary to primary neurologic abnormalities), can reflect the severity of the condition, and in many cases is associated with and likely contributing to worsening of the clinical condition, increasing the potential for life-threatening cardiac arrhythmias and death. Because cardiac autonomic function involves numerous molecular processes, use of radiotracers for imaging is an ideal method of assessment.

CARDIAC NEURONAL ANATOMY

Cardiac neural autonomic function is controlled by regulatory centers in the midbrain, hypothalamus, pons, and medulla that integrate input signals from other parts of the brain and receptors throughout the body. From the brain, efferent signals follow descending pathways in the spinal cord, and synapse with preganglionic fibers that leave the spinal cord at levels T1–L3, subsequently synapsing with paravertebral stellate ganglia. Left stellate postganglionic fibers innervate the right ventricle, whereas right postganglionic fibers innervate anterior and lateral left ventricle. In the heart sympathetic nerves follow the coronary arteries in the subepicardium and then penetrate the myocardium. The major chemical mediator of sympathetic function is NE.[1,2]

Parasympathetic fibers are scarce in comparison with sympathetic fibers. They originate in the medulla and follow the vagus nerves. In the heart they start epicardially, cross the atrioventricular (AV) groove, and penetrate the myocardium, located thereafter in the subendocardium. Parasympathetic output controls sinoatrial and AV nodal function. Parasympathetic fibers predominantly innervate the atria and are scare in the ventricle (densest in the inferior wall). The chemical mediator of parasympathetic function is acetylcholine.

Most published literature and current clinical applicability of autonomic radionuclide imaging is of the sympathetic system, with parasympathetic imaging studies limited mostly to animals. The following discussion therefore deals predominantly with cardiac sympathetic imaging.

RADIONUCLIDE TRACERS FOR IMAGING CARDIAC SYMPATHETIC INNERVATION

Imaging of cardiac sympathetic innervation focuses on the synaptic junction, shown in **Fig. 1**. Most of the radiotracers developed and investigated to this point image presynaptic anatomy and function, although newer tracers that bind to postsynaptic α and β receptors are also being designed and investigated. All cardiac neuronal radiotracers are considered investigational for cardiac imaging at the time of this writing.

The sympathetic mediator NE is synthesized by a series of steps originating with tyrosine, and is stored at high concentrations in presynaptic

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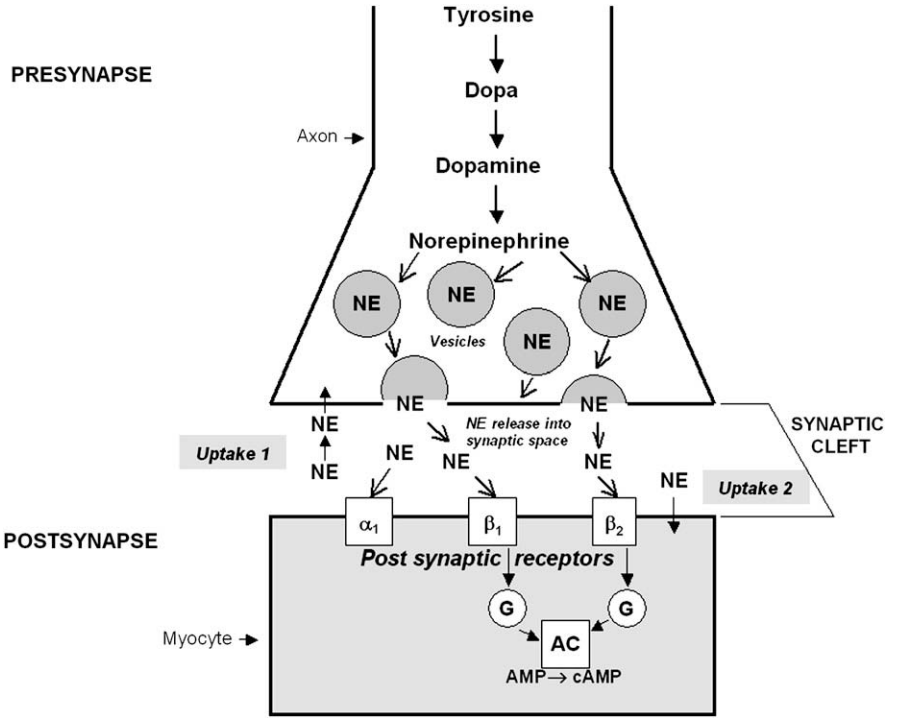

Fig. 1. Sympathetic neuronal synapse. AC, adenyl cyclase; AMP, adenosine monophosphate; cAMP, cyclic adenosine monophosphate; G, G proteins; NE, norepinephrine.

vesicles. In response to a stimulus, the NE-containing vesicles are released into the synaptic space and bind to postsynaptic β_1, β_2, and α receptors, enhancing adenyl cyclase activity through intermediary G proteins, resulting in the desired cardiac stimulatory effects.[3,4] As part of tight control of sympathetic physiology, NE is then taken back up into the presynaptic terminal by way of a transporter protein–mediated, sodium-, energy-, and temperature-dependent process (ie, ''uptake-1'') for storage or catabolic disposal, in effect terminating the sympathetic response. Some synaptic NE is also taken up by the nonneuronal postsynaptic cells, probably by sodium-independent passive diffusion (ie, the ''uptake-2'' system).[5,6]

Synthesis and administration of radiolabeled modifications or radiolabeled analogs of the various molecules along the NE production pathway allows imaging along with qualitative and quantitative assessment of neuron function. For example, a radiolabeled modification of the intermediary compound dopamine (ie, ^{18}F-dopamine) has shown promise as a potential PET agent for neuronal imaging.[7] Most of the experimental and clinical work on neuronal imaging has been with radiolabeled analogs, both single photon emission computed tomography (SPECT) and positron emission tomography (PET), of the end product, NE. Guanethidine is a false neurotransmitter analog of NE that when administered is taken up by the uptake-1 pathway. Chemical modification of guanethidine produces a molecule that can be labeled with radioactive iodine—meta-iodobenzylguanidine (*m*IBG)—and therefore imaged. When first developed in the late 1970s, *m*IBG was labeled with ^{131}I and was used for detection of neural crest tumors, neuroblastomas, and pheochromocytomas. ^{131}I-*m*IBG imaging of such tumors is at the time of this writing the only US Food and Drug Administration (FDA)–approved use of radiolabeled *m*IBG in the United States. Because ^{131}I gives off relatively high-energy (365 keV) γ emissions, emits β^- particles, and has a relatively long half-life of about 8.02 days, ^{123}I labeling has been developed and is preferred. ^{123}I emits predominantly γ photons with energies of 159 keV and has a half-life of 13.2 hours, therefore being easily imaged and well tolerated. ^{123}I-*m*IBG has been used extensively in Europe and Japan for cardiac imaging, but is currently not FDA approved in the United States for cardiac imaging and is therefore considered to be investigational.

As an analog of NE and guanethidine, intravenously administered ^{123}I-*m*IBG diffuses into the