The study entitled "An Intrinsic Adrenergic System in Mammalian Heart," published in this issue of *The Journal*, goes farther and more convincingly than any previous work to support the functional significance of an "intrinsic cardiac adrenergic system." Huang et al. (1) document the presence of clusters of adrenergic cardiac cells devoid of the characteristic axonal elements of neurons. These cells can synthesize and release catecholamines in the absence of innervation and increase the rate of contraction of isolated myocytes in culture.

In this editorial I will briefly review (*a*) our current concept of cardiac regulation; (*b*) selected previous work on adrenergic cardiac cells; (*c*) the uniqueness of the study by Huang et al.; and (*d*) the new questions that the study has provoked.

Cardiac regulation

The regulation of cardiac function is dependent on two systems. The first is the "extrinsic neurohumoral" control, predominantly through the sympatho-adrenal system (2). The second is an "intrinsic myogenic" regulation inherent to the cardiac myocyte and reflected in the dependence of myocardial performance on a change in length or preload of myocardial fibers, manifested by the well-known Frank-Starling mechanism (3); a change in afterload, often referred to as the Anrep effect (4); and a change in frequency of contraction, known as the staircase or Treppe phenomenon (5).

The presence of a third system which is, on the one hand, intrinsic to the heart but not to the myocytes, and on the other hand, adrenergically mediated yet independent of autonomic innervation, has been suspected based on ultrastructural and enzymatic studies (6–10). The work by Huang et al. (1) provides support for such a system and for its functional significance.

Adrenergic cells

Cardiac chromaffin cells were described in the 1930s (6, 7) and more recently they were shown to contain biogenic amines (8). They are distinct from the cardiac ganglion cells and their true function was never defined. Jacobowitz (8) proposed that they represent an extraneuronal catecholamine pool that may be influenced by cholinergic innervation from nearby parasympathetic ganglion cells. These catecholaminergic cells could also in turn exert a paracrine influence by releasing their catecholamines which would inhibit ganglionic transmission (8). However, Ellison and Hibbs (9) were unable to demonstrate the communications necessary to postulate such a negative feedback. Despite the debate about their precise function, there was convincing evidence in 1990 by Elayan et al. (11) that cardiac tissue homogenates, from rats with prior adrenal demedullation treated with 6-hydroxydopamine to destroy sympathetic innervation, could synthesize up to one-third of the total cardiac content of adrenaline. These findings established a nonneuronal cardiac origin of adrenaline. Furthermore, the presence of adrenaline in blood and urine of patients who have undergone bilateral adrenalectomy (12, 13) and the significant increase in adrenaline release from the hearts of patients with heart failure (14), occurring independently of sympathetic nerve stimulation, support the extraadrenal cardiac origin of the hormone in humans. With our recent appreciation of the role of prejunctional β2 receptors in the release of norepinephrine from nerve terminals (15, 16), one can postulate a significant paracrine influence of the adrenaline released from clusters of adrenergic cardiac cells on sympathetic presynaptic transmission from sympathetic nerves.

Uniqueness of the Huang et al. study

Their study demonstrates several strengths. First, the use of magnetic beads to isolate for the first time the cardiac adrenergic cells from myocytes provides the capability of comparing the adrenergic cells to myocytes and to sympathetic neurons with respect to morphology, catecholamine content and release, and enzyme content and message. The approach allowed the authors to define with precision and purity of preparation the distinctiveness of the intrinsic cardiac adrenergic (ICA) cells and their unequivocal capacity to synthesize catecholamines in a system totally devoid of innervation. Second, the identification of ICA cells in human fetal hearts at a developmental stage preceding sympathetic innervation coupled with the results of the study by Zhou et al. (17), in which targeted destruction of the tyrosine hydroxylase gene in mice caused midgestational death with phenotypic anomalies of the heart, suggests a major function for these adrenergic cells in cardiac development. Third, the coculture system, which demonstrated that the constitutively released catecholamines from ICA cells could induce an increase in rate of contraction of cardiac myocytes which is blocked by a β blocker, supports the putative functional significance of this system in cardiac regulation. It is unlikely that the catecholamine release in the ICA cell/neonatal myocyte coculture from 4–5-d-old rats was due to contamination from sympathetic nerve endings for several reasons. First, there were no axonal structures nor sympathetic nerve endings by immunohistochemistry or electron microscopy. Second, neonatal rats do not exhibit a functionally active sympathetic nervous system until they are 2 wk old (18), and any residual endings would have degenerated in the primary culture system as it was kept for 5 d to allow confluence of myocytes prior to study. Third, the release of three catecholamines (norepinephrine, epinephrine, and dopamine) is not characteristic of sympathetic endings which release primarily norepinephrine.

New questions provoked by the work

The first and most provocative question is, What kind of cells are these? How unique are they? They fail to grow neurites or axons after several days in culture yet they stain positively with neuron-specific enolase and with another neuroendocrine marker: the protein gene product 9.5 (PGP 9.5) (19). Their cytoplasmic clear vesicles establish their secretory capacity but distinguish them from the usually dense granules of sympathetic nerve terminals or chromaffin cells. Clear vesicles may indicate the presence of peptides, or nonpeptide mediators that are not adrenergic, in addition to the catecholamines.

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The cells described by Huang et al. (1) also differ from the densely granulated adrenal medullary cells. The adrenal medulla is innervated by preganglionic sympathetic nerve endings that are cholinergic-nicotinic. The release of adrenaline from the adrenal gland is under neural control. In contrast, the ICA cells do not require innervation to release catecholamines.

Another specific feature of ICA cells is their apparently ubiquitous distribution in both atria and ventricles in contrast to the catecholamine-containing cells described by Ellison and Hibbs (9) in the atria and A-V node of guinea pig hearts. Ellison and Hibbs have proposed that those cells have become more concentrated during phylogeny to the atria and A-V nodes.

The proximity of the ICA cells to blood vessels raises questions regarding their chemosensitivity, their possible role as cardiac chemoreceptors, and the influence of nicotine, histamine, or circulating peptides on the regulation of their release of catecholamines.

A second question addresses the issue of the phenotypic change that may occur in the cells described by Huang et al. (1) as they progress from the fetal stage, where their role might be primarily developmental, to the neonatal and adult stages where their regulatory cardiac function may be important. Conceivably, they might provide a substitute adrenergic support system following sympathetic denervation in transplanted hearts. Depending on their location, the clusters of adrenergic cells may also modulate parasympathetic ganglionic transmission or sympathetic prejunctional norepinephrine release.

Studies in denervated adult hearts would be important in defining the balance and interplay between this intrinsic adrenergic system and the extrinsic nonadrenergic neural system. Would the catecholamine content or density of the ICA cells increase following denervation? Do the ICA cells divide in culture in the absence of innervation? Would the coculture of ICA with sympathetic neurons modify their phenotypic expression?

To summarize, Huang et al. (1) have presented us with a distinct cardiac adrenergic cell system present in fetal, neonatal, and adult hearts of rats and humans. The cells can synthesize and release catecholamines independent of sympathetic innervation. Their putative roles in cardiac development and in the regulation of cardiac function are compelling. The degree to which this new intrinsic cardiac adrenergic system will complement, substitute for, or modulate either the extrinsic autonomic neurohumoral control or the intrinsic myogenic regulation, or both, remains to be determined.

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