The enhanced stimulation and outflow of catecholamines has long been recognized as an important mechanism in the progression of heart failure (1). In 1984, Cohn et al. (2) established that higher plasma concentrations of norepinephrine predicted worse survival in patients with heart failure. These studies and others led to the initial clinical trials to block catecholamines from binding to β-adrenergic receptors (β-AR) in the heart (3). A promising small molecule that inhibits the β-adrenergic signaling cascade in the heart and decreases circulating catecholamines in a preclinical model is presented in the Journal this week from Kamal and colleagues (4).

Norepinephrine binds to the β-ARs in the heart and increases contraction (5). In heart failure, the persistent catecholamine-mediated activation of β-ARs leads to receptor phosphorylation, desensitization, and down-regulation (5). Phosphorylation of the β-ARs is mediated by a G-protein-coupled receptor (GPCR) kinase, GRK2 (6). GRK2 belongs to a family of GPCR kinases (6). GRK2 is recruited to the β-ARs in the plasma membrane via activated G-protein βγ (Gβγ) subunits (6). Blockade of GRK2 is cardioprotective in pre-clinical models (5). A peptide encoding the 194–amino acid domain of GRK2, named βARKct (GRK2 is also known as βARK1), blocks GRK2, and improves cardiac function in larger animals and inhibits the progression of cardiac failure in mice (5). The study from Kamal and et al. (4) also targets GRK2, and appears to have additional influence on lowering catecholamine levels.

Chidsey, Braunwald, and Morrow were the first to publish that norepinephrine excretion in the urine was elevated in patients with heart failure (7). The medullary chromaffin cells in the adrenal glands release catecholamines (norepinephrine and epinephrine). Pioneering work from Esler provided evidence that in healthy individuals approximately 30% of the norepinephrine in the plasma comes from nerves in the lungs, 25% from the nerves in the kidneys, 20% to 25% from nerves in skeletal muscle, 5% to 7% from the hepatomesenteric circulation, 6% from the skin, 4% from the brain, 3% from the heart, and 2% to 3% from the adrenal medulla (8). Norepinephrine originating from these tissues is referred to as spillover, or overflow. Overflow of norepinephrine (that which is not taken up by neurons, extraneuronal sites, or metabolized) is released into the venous outflow. The precise origin(s) of norepinephrine spillover in heart failure remains a mystery; however, spillover has been identified in the heart, kidneys, and skeletal muscle (9–11). Reduced clearance of catecholamines due to the decrease in cardiac output also contributes to the increase in plasma catecholamines in patients with heart failure (1). A significant increase is also seen in the adrenal gland activity in patients with heart failure (9,12).

Excessive norepinephrine is directly toxic to the heart and is believed to be central to the neurohormonal hypothesis that exuberant sympathetic activity drives at least part of the pathophysiology of chronic heart failure. Strategies to reduce sympathetic overproduction by pharmacologically activating central α2-adrenergic receptors (α2-AR) or imidazoline-1 receptors have been tested in patients with heart failure. Moxonidine, a selective imidazoline-1 receptor activator, strikingly lowers plasma sympathetic activity in heart failure, but had an adverse mortality effect in patients with heart failure (13). Clearly, significantly reducing sympathetic activity in heart failure is not by itself successful, but how one reduces sympathetic drive may be highly important.

Norepinephrine and epinephrine release from the adrenal gland is regulated through a feedback inhibition loop that involves phosphorylation of the α2-AR (14). In 2007, Lymeropoulos et al. showed evidence that this feedback inhibition loop to decrease the release of norepinephrine was dysregulated in pre-clinical models of heart failure (15). Specifically, this discovery showed that GRK2 up-regulation in the adrenal gland was the mechanism responsible for phosphorylating and desensitizing the α2-AR, thereby...
removing the feedback inhibition loop and creating the sympathetic overdrive in heart failure.

In this week's issue of the Journal, Kamal et al. (4) used a novel small molecule that inhibits GRK2 by binding to a specific protein–protein interaction domain of GRK2 that binds Gβγ (4). This small molecule, gallein, was identified through a novel compound screen (16). Gallein was administered daily 4 weeks after transverse aortic constriction in mice (a pressure overload model) and continued for 8 weeks. Gallein improved survival, enhanced cardiac function, and inhibited cardiac hypertrophy (4). In the heart, gallein restored β-AR density and decreased GRK2 expression (4). In the circulation, gallein reduced plasma epinephrine and norepinephrine concentrations (4). Adrenal glands from transverse aortic constriction mice treated with gallein and cultured in vitro showed lower levels of basal catecholamine secretion (4). It is not clear from these studies what fraction of the circulating catecholamine concentration that is being reduced by gallein is from the adrenal glands (4). α2-ARs are also expressed in presynaptic sympathetic nerve terminals; therefore, it is conceivable that these receptors are also targeted by gallein. Of note, the density of α2-ARs in the central nervous system is an order of magnitude higher than those in the adrenal chromaffin cells (17). Future studies may need to address this issue.

It should be remembered that cardiac myocyte membrane β-AR desensitization and down-regulation are highly conserved natural mechanisms that may protect the heart from excessive catecholamine stimulation. If gallein reduces circulating plasma catecholamines while simultaneously restoring cardiac membrane β-AR density, then this strategy may in principle improve the inotropic state. Additional studies will eventually be necessary to investigate this further.

Currently, β-blockers are a mainstay of heart failure therapy and have proven efficacy to reduce mortality and morbidity in heart failure (3). The report by Kamal et al. (4) suggests that a new small molecule targeting GRK2 may have additional beneficial actions in the adrenal gland and possibly on inhibition of inflammation. However, obstacles remain. GRK2 is ubiquitously expressed, and gallein might have several off-target effects (i.e., the brain), leading to unforeseen outcomes not observed in the relatively short-term treatment in the current study. The cross-disciplinary team of Smrcka and Blaxall are leaders in the field and a tour de force in small molecule screening and β-adrenergic signaling. We look forward to additional pre-clinical and clinical replication from this group and others.

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