



Cardiac hypertrophy: stressing out the heart

Jil C. Tardiff

Albert Einstein College of Medicine, Yeshiva University, Bronx, New York, USA.

The question of what differentiates physiological from pathological cardiac hypertrophy remains one of the most clinically relevant questions in basic cardiovascular research. The answer(s) to this question will have far-ranging importance in the fight against hypertrophic heart disease and failure. In this issue of the *JCI*, Perrino et al. have used a unique model system to mimic the pathophysiologic effects of an intermittent pressure overload on the heart — in effect, to examine the basic issue of what determines an in vivo pathogenic stimulus (see the related article beginning on page 1547). Their findings clearly show that it is the nature of the inciting stimulus, as opposed to chronicity, that establishes the initial pathogenic response and that a distinct disruption of the β -adrenergic system is centrally involved in the earliest alterations of myocellular physiology. These results suggest both a new paradigm for treatment options in hypertrophic cardiac disease and novel methodologies for further studies.

In order to maintain sufficient cardiac output over an expected lifespan of 70-plus years, the heart must respond to a myriad of physiologic and pathophysiologic stimuli. To meet these physiological demands on a day-to-day basis the heart relies on a phenomenon known as myocardial reserve, whereby it can reversibly alter cardiac output in response to a sudden increase in demand via a broad range of myocellular signaling pathways anchored, in part, by the β -adrenergic system. It has long been noted, however, that sustained or progressive demands on the heart can result in cardiac hypertrophy (1). Many common disease states lead to the prolonged increase in hemodynamic demand (either pressure- or volume-based) that causes the characteristic pathogenic myocellular hypertrophy including hypertension, valvular abnormalities, and post-myocardial infarction remodeling (2). In the pressure-overloaded state, the heart maintains cardiac output in the context of elevated afterload by increasing ventricular wall thickness as dictated by the Law of Laplace. The end result, however, is only a short-term solution. If the inciting pathogenic stimulus is not relieved, the “adap-

tive” increase in myocellular mass leads to impaired ventricular relaxation, filling, and, in many cases, eventual cardiac failure. Thus given the continuing high incidence of inciting disorders and the resultant profound degree of associated morbidity and mortality, understanding the pathogenesis of hypertrophic heart disease remains a central focus of cardiovascular research (3).

Cardiac hypertrophy can be adaptive or maladaptive

It has long been noted that ventricular enlargement does not necessarily lead to a decrease in cardiac performance. In fact, numerous studies dating back nearly 40 years have demonstrated that the mild to moderate left ventricular hypertrophy observed in highly trained athletes actually enhances cardiac performance via increases in stroke volume, contractility, and oxygen consumption with preserved relaxation (4, 5). This surprising observation, that similar degrees of left ventricular hypertrophy could exhibit strikingly different profiles of cardiovascular function, led to a series of animal studies that began to establish the link between whole-heart and myocellular physiology. Early results revealed significant differences in myosin isoform distribution, myofibrillar ATPase activity, and cardiac function between aortic-banded and exercise-trained rats, thus establishing the early groundwork for the molecular basis of primary cardiac disease (6). Fast-forward 30 years and the availability of elegantly designed cardiac-restricted transgenic and knockout mice, sophisticat-

ed in vivo physiologic measurements, and an extensive knowledge of myocellular signaling pathways have converged to finally begin to comprehensively delineate the basic mechanisms that differentiate physiologic from pathologic hypertrophy (7, 8).

The nature of the pathogenic stimulus determines the cardiac response — chronicity is not sufficient

In this issue of the *JCI*, Perrino et al. (9) use a unique model system to address some of the more intractable questions regarding the nature of pathogenic stimuli and the resultant cardiovascular responses that determine the clinical course of hypertrophic heart disease.

The first set of studies was designed to determine the influence of the nature and duration of the cardiovascular stimulus on the development of cardiac hypertrophy in mice using a unique modification of transverse aortic constriction (TAC), known as intermittent TAC (iTAC), that allows for the controlled and intermittent application of a pathogenic pressure overload. Interestingly, 4 weeks of iTAC performed in tandem with chronic pressure overload by chronic TAC (cTAC) and independent forms of exercise (i.e., forced swimming and voluntary wheel running) resulted in a distinct and somewhat surprising pattern of ventricular remodeling characterized by mild hypertrophy in the absence of fetal gene induction, preserved global LV function, and a marked decrease in capillary density. This seemingly intermediary phenotype (sharing components of the cTAC and exercise groups) at the whole-heart and tissue levels is in stark contrast to the cellular findings, in which isolated ventricular myocytes from iTAC mice demonstrated significantly impaired contractility and relaxation parameters both at baseline and in response to β -agonist exposure similar to those observed in cTAC myocytes.

These complex results highlight the profound specificity of the likely sarcolemmal “sensor(s)” that transduce the nature of the input stimulus to the cardiovascular response. Moreover, the fact that intermittent exposure to a pathogenic stimulus was sufficient to dissociate the global hyper-

Nonstandard abbreviations used: β AR, β -adrenergic receptor; β ARK1, β AR kinase 1; cTAC, chronic TAC; EDPVR, end-diastolic pressure–volume relationship; ISO, isoproterenol; iTAC, intermittent TAC; iTAC_{Y^{inact}}, cardiac-specific overexpression of PI3K_{Y^{inact}}; PI3K_{Y^{inact}}, catalytically inactive PI3K_Y; TAC, transverse aortic constriction.

Conflict of interest: The author has declared that no conflict of interest exists.

Citation for this article: *J. Clin. Invest.* 116:1467–1470 (2006). doi:10.1172/JCI28884.

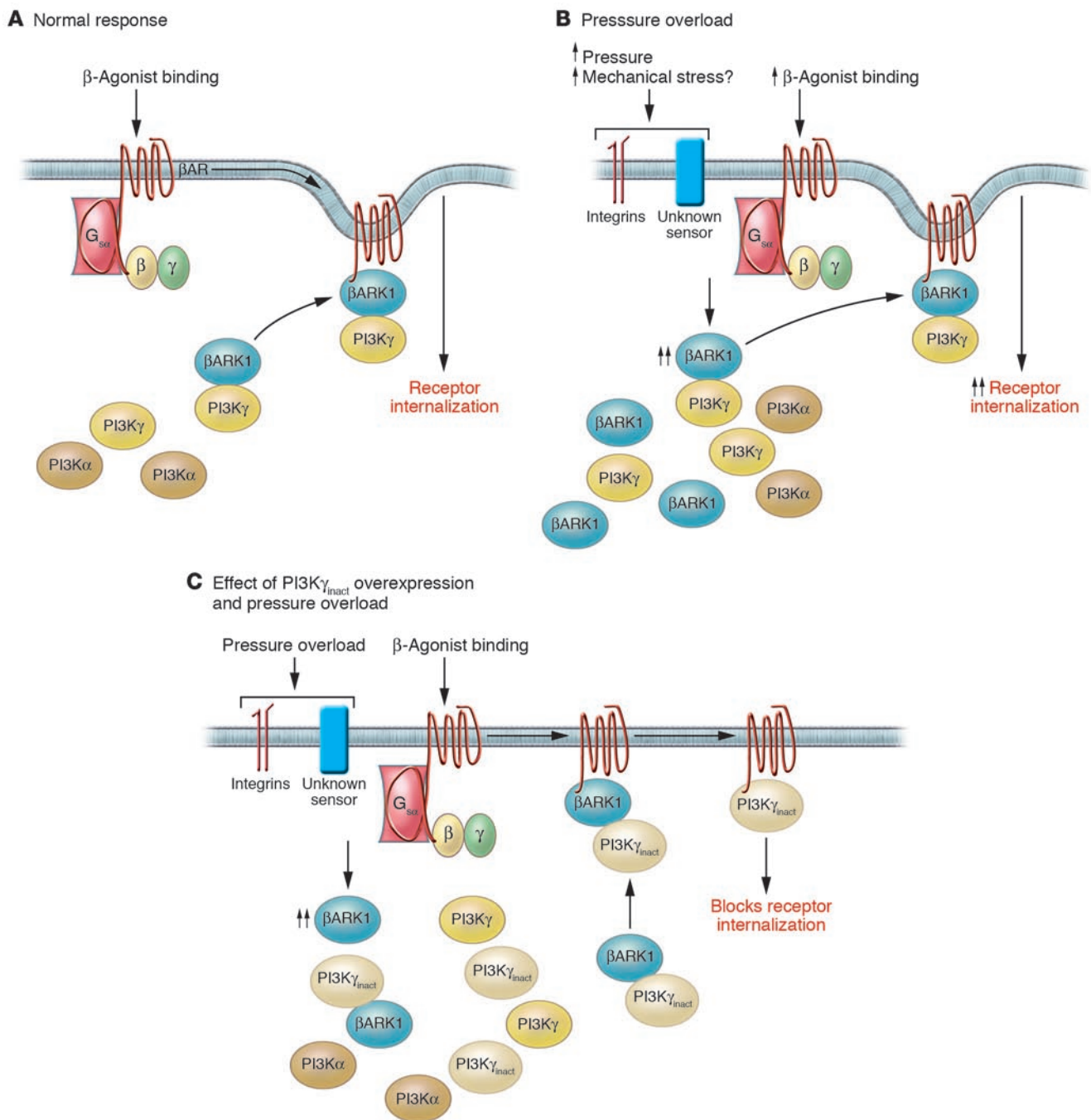


Figure 1

Potential mechanism for the role of early β AR dysfunction in the hypertrophy-independent pathological phenotype induced by iTAC. **(A)** Role of PI3K γ in modulating β AR internalization. Chronic β -agonist binding to β ARs leads to an induction in myocellular β ARK1 levels. β ARK1 binds to PI3K γ and facilitates its translocation to the receptor complex, where the subsequent generation of D-3 phosphoinositides leads to the recruitment of multiple adapter proteins and receptor internalization. **(B)** Intermittent pressure overload (iTAC) promotes early β AR dysfunction. Normal mice exposed to both 1 week and 4 weeks of iTAC exhibited significant β AR downregulation and desensitization. In the case of the 1-week iTAC mice, this effect was seen despite normal steady-state catecholamine levels and highlights the pathogenic nature of the pressure-overload stimulus. While the pressure-overload sensor mechanism is not fully understood, the participation of the molecules involved in mechanical stress (e.g., integrins) is likely. These 2 stimuli result in the observed pathogenic response, including a significant induction of β ARK1 levels causing an increase in PI3K γ translocation to the agonist-bound receptor complex and subsequent increase in receptor internalization. **(C)** Overexpression of PI3K γ_{inact} in the heart reverses the downregulation of β ARs and the early pathogenic changes in iTAC mice. Unlike normal mice, iTAC γ_{inact} mice subjected to 1 week of iTAC exhibited normal β AR density and β AR/ G_s coupling in the context of elevated β ARK1. Overexpression of PI3K γ_{inact} leads to a competitive displacement of all PI3K isoforms from the β ARK1/PI3K complex. This displacement blocks the effects of the early induction of β ARK1 caused by iTAC and effectively preserves β AR levels and function.



trophic phenotype (mild) from the cellular phenotype (moderate to severe) in iTAC mice was striking; not only does this finding support several recent studies in which the pathogenic cardiovascular response was separated from myocellular growth, it extends our understanding of the central role of the nature of the inciting stimulus (10–12). Thus, these results definitively show that while the duration of the discrete pathogenic stimulus may dictate the magnitude of ventricular hypertrophy, chronicity is not sufficient to cause hypertrophic heart disease — the nature of the inciting stimulus must be pathogenic.

Early β -adrenergic receptor system dysfunction drives the pathogenic hypertrophic phenotype

Based on their initial findings (9), the authors were able to use the specificity of the iTAC stimulus to begin to address both the timing and the potential mechanisms of the pathogenic cardiovascular response to intermittent overload. As recently noted in an excellent review by Dorn and Force, one of the inherent difficulties in studying the primary mechanisms involved in the development of cardiac hypertrophy and heart failure lies in the complex interplay among the intersecting protein kinase cascades that regulate both physiologic and pathologic hypertrophy (13). This complexity limits the utility of studying late-stage cardiac tissue to determine cause and effect.

In their initial 4-week studies, Perrino et al. (9) showed that only the mouse hearts exposed to pressure overload (iTAC and cTAC) exhibited abnormalities in the β -adrenergic receptor (β AR) system (Figure 1). Specifically, they observed similar decreases in β AR density with a corresponding loss in isoproterenol-dependent (ISO-dependent) cAMP generation and a concomitant increase in β AR kinase 1 (β ARK1) levels and β ARK1-associated PI3K γ . Previous work by this group and others had demonstrated that PI3K γ decreases both cardiac contractility via inhibition of β 2AR-associated adenylate cyclase and attenuation of β 2AR internalization (14–16). Building on these observations, the authors then directly addressed the basic question of whether the observed derangements in β AR-mediated pathways were *causally* involved in iTAC pathology by examining the early prehypertrophic changes induced by 1 week of either pathologic (iTAC, cTAC) or physiologic stimuli (9). This elegant series of in

vivo studies using a previously described transgenic mouse model (iTAC γ_{inact} mice, which express a catalytically inactive form of PI3K γ [PI3K γ_{inact}] that displaces the endogenous PI3K γ) revealed that the inhibition of β ARK1-mediated PI3K recruitment to ligand-activated receptors (and thus the maintenance of β AR function) abrogated a significant subset of the prehypertrophic functional and structural changes induced by iTAC.

Of note, while treatment with the β AR-blocking agent metoprolol recapitulated many aspects of this apparent rescue via PI3K γ_{inact} overexpression, including preserved β AR levels and coupling as well as a decrease in hypercontractility and in the slope of the end-diastolic pressure–volume relationship (EDPVR), no effect was seen on either vascular rarefaction or the decrease in the rate of isovolumic relaxation — further evidence that the complex early pathogenic response to pressure overload may involve additional G protein-independent signaling pathways. Finally, while acute plasma catecholamine levels from matched sets of swimming, iTAC, and iTAC γ_{inact} mice were equivalent, only the iTAC mice exhibited evidence of “pure” β AR uncoupling to G_s subunits (e.g., in the context of normal receptor levels), a provocative result that suggests that the observed early β AR desensitization is not due solely to the marked increase in sympathetic activation, but is highly dependent on the nature of the pathogenic pressure overload.

A potentially broader paradigm to spur new approaches to an old problem

The compelling findings presented by Perrino et al. (9) regarding the ability of controlled intermittent pressure overload to finely dissociate multiple aspects of the regulation of pathogenic hypertrophy and the central role of early β -adrenergic dysfunction provide both a new framework for further investigation and a new in vivo methodology. Like all new answers to old problems, this work raises a host of interesting questions. First, it remains unclear what constitutes the pathogenic nature of the intermittent pressure overload. One possibility is that, unlike the increase in venous return and oxygen demand that occurs with exercise, the establishment of an acute pressure overload for even a short period of time cannot be overcome by any of the normal cardiovascular responses. The heart is, in effect, defenseless against

such an assault. The nearly immediate uncoupling of the β AR, rapid development of significant vascular rarefaction, hypercontractility, and impaired relaxation in the iTAC mice is consistent with a “surrender” phenotype. It would be interesting to determine whether a different time course of applied intermittent pressure overload would alter the observed phenotype.

Another question involves the identity of the actual trigger, or sensor, of the pressure overload. The 7-day studies clearly establish that the pathogenic phenotype in iTAC can be fully dissociated from hypertrophic growth in the context of early β AR dysfunction and is not fully dependent on neurohormonal stimulation. In this context, the specificity of the response is striking. While the central role of integrins and stretch-activated channels in transducing mechanical stretch into the activation of downstream pathways and kinase cascades has been well established, the proteins or structures that actually sense stretch remain unknown. Activation of myocellular remodeling via alterations in biomechanical stretch (mechanotransduction) plays an important role in many cardiomyopathies including those caused by postinfarction remodeling and mutations in cytoskeletal and sarcomeric proteins (17). Indeed, animal models of both dilated and hypertrophic cardiomyopathies (representing intrinsic mechanical stress) have demonstrated a similar dissociation between myocellular pathology and growth, as seen in the iTAC mice (12, 18). Thus, both extrinsic and intrinsic pathologic stimuli may activate similar myocellular responses involving both G protein-dependent and -independent signaling pathways.

Finally, from the clinical standpoint the current studies (9) fully expose the inherent limitations in using cardiac hypertrophy as a noninvasive prognostic indicator. The importance of decreasing LV mass during antihypertensive therapy has been clearly shown to decrease the rate of clinical endpoints; indeed, based on the results in the current paper, the aggressive treatment of hypertension as a means of directly decreasing the pathogenic stimulus of the perceived pressure load is an important therapeutic goal (19). The markedly abnormal phenotype of the iTAC mice (after both 7 days and 4 weeks of exposure to the intermittent pressure load) in the absence of either the reactivation of the fetal gene program or a large increase in ventricular mass was surprising and, frankly, sober-



ing from a clinical standpoint. It is reminiscent of the oft-noted clinical findings in hypertrophic cardiomyopathy wherein the degree of diastolic impairment is often described as “out of proportion” to the observed ventricular hypertrophy, thus suggesting a significant myocellular contribution to disease pathogenesis. It is interesting to speculate that the well-known salutary effects of postinfarction treatment with metoprolol may reflect the molecular findings in the current paper. Thus the results presented by Perrino et al. lay the groundwork for a robust 2-pronged therapeutic approach based on relief of the inciting pathogenic stimulus and direct treatment of the underlying molecular derangements, perhaps via novel compounds to displace active PI3K isoforms from the receptor complex.

Address correspondence to: Jil C. Tardiff, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Ullmann Building, Room 316, Bronx, New York 10461, USA. Phone: (718) 430-8914; Fax: (718) 430-8819; E-mail: tardiff@aecom.yu.edu.

1. Meerson, F.Z. 1962. Compensatory hyperfunction of the heart and cardiac insufficiency. *Circ. Res.* **10**:250–258.
2. Lorell, B.H., Apstein, C.S., Weinberg, E.O., and Cunningham, M.J. 1990. Diastolic function in left ventricular hypertrophy: clinical and experimental relationships. *Eur. Heart J.* **11**(Suppl. G):54–64.
3. Ho, K.K., Pinsky, J.L., Kannel, W.B., and Levy, D. 1993. The epidemiology of heart failure: the Framingham Study. *J. Am. Coll. Cardiol.* **22**:6A–13A.
4. Raskoff, W.J., Goldman, S., and Cohn, K. 1976. The “athletic heart”. Prevalence and physiological significance of left ventricular enlargement in distance runners. *JAMA.* **236**:158–162.
5. Bevegard, B.S., and Shepherd, J.T. 1967. Regulation of the circulation during exercise in man. *Physiol. Rev.* **47**:178–213.
6. Giusti, R., Bersohn, M.M., Malhotra, A., and Scheuer, J. 1978. Cardiac function and actomyosin ATPase activity in hearts of conditioned and deconditioned rats. *J. Appl. Physiol.* **44**:171–174.
7. Wilkins, B.J., et al. 2004. Calcineurin/NFAT coupling participates in pathological, but not physiological, cardiac hypertrophy. *Circ. Res.* **94**:110–118.
8. Barki-Harrington, L., Perrino, C., and Rockman, H.A. 2004. Network integration of the adrenergic system in cardiac hypertrophy. *Cardiovasc. Res.* **63**:391–402.
9. Perrino, C., et al. 2006. Intermittent pressure overload triggers hypertrophy-independent cardiac dysfunction and vascular rarefaction. *J. Clin. Invest.* **116**:1547–1560. doi:10.1172/JCI25397.
10. Shioi, T., et al. 2000. The conserved phosphoinositide 3-kinase pathway determines heart size in mice. *EMBO J.* **19**:2537–2548.
11. Frey, N., et al. 2004. Mice lacking calcineurin-1 are sensitized to calcineurin signaling and show accelerated cardiomyopathy in response to pathological biomechanical stress. *Nat. Med.* **10**:1336–1343.
12. Ertz-Berger, B.R., et al. 2005. Changes in the chemical and dynamic properties of cardiac troponin T cause discrete cardiomyopathies in transgenic mice. *Proc. Natl. Acad. Sci. U. S. A.* **102**:18219–18224.
13. Dorn, G.W., 2nd, and Force, T. 2005. Protein kinase cascades in the regulation of cardiac hypertrophy. *J. Clin. Invest.* **115**:527–537. doi:10.1172/JCI200524178.
14. Nienaber, J.J., et al. 2003. Inhibition of receptor-localized PI3K preserves cardiac β -adrenergic receptor function and ameliorates pressure overload heart failure. *J. Clin. Invest.* **112**:1067–1079. doi:10.1172/JCI200318213.
15. Naga Prasad, S.V., Esposito, G., Mao, L., Koch, W.J., and Rockman, H.A. 2000. Gbetagamma-dependent phosphoinositide 3-kinase activation in hearts with in vivo pressure overload hypertrophy. *J. Biol. Chem.* **275**:4693–4698.
16. Crackower, M.A., et al. 2002. Regulation of myocardial contractility and cell size by distinct PI3K-PTEN signaling pathways. *Cell.* **110**:737–749.
17. Mann, D.L. 2005. Left ventricular size and shape: determinants of mechanical signal transduction pathways. *Heart Fail. Rev.* **10**:95–100.
18. Knoll, R., et al. 2002. The cardiac mechanical stretch sensor machinery involves a Z disc complex that is defective in a subset of human dilated cardiomyopathy. *Cell.* **111**:943–955.
19. Devereux, R.B., et al. 2004. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA.* **292**:2350–2356.

Mechanisms of sympathoadrenal failure and hypoglycemia in diabetes

Philip E. Cryer

Division of Endocrinology, Metabolism and Lipid Research, General Clinical Research Center, and Diabetes Research and Training Center, Washington University School of Medicine, St. Louis, Missouri, USA.

A reduced sympathoadrenal response, induced by recent antecedent hypoglycemia, is the key feature of hypoglycemia-associated autonomic failure (HAAF) and, thus, the pathogenesis of iatrogenic hypoglycemia in diabetes. Understanding of the mechanism(s) of that reduced response awaits new insight into its basic molecular, cellular, organ, and whole-body physiology and pathophysiology in experimental models. In this issue of the *JCI*, McCrimmon and colleagues report that application of urocortin I (a corticotrophin-releasing factor receptor–2 agonist) to the ventromedial hypothalamus reduces the glucose counterregulatory response to hypoglycemia in rats (see the related article beginning on page 1723). Thus, hypothalamic urocortin I release during antecedent hypoglycemia is, among other possibilities, a potential mechanism of HAAF.

Nonstandard abbreviations used: HAAF, hypoglycemia-associated autonomic failure; T1DM, type 1 diabetes mellitus; VMH, ventromedial hypothalamus.

Conflict of interest: The author has served on advisory boards of Novo Nordisk Inc., Takeda Pharmaceuticals North America Inc., and MannKind Corp. in recent years.

Citation for this article: *J. Clin. Invest.* **116**:1470–1473 (2006). doi:10.1172/JCI28735.

The clinical problem of iatrogenic hypoglycemia in people with diabetes mellitus (1) has stimulated bidirectional translational research. That included, initially, patient-oriented research based on the then-existing body of knowledge and, more recently, basic research into the molecular, cellular,

organ, and whole-body physiology of glucose counterregulation — the mechanisms that normally prevent or rapidly correct hypoglycemia — and its pathophysiology in experimental models (2). The latter is exemplified by the report from McCrimmon and colleagues (3) in this issue of the *JCI*. In the aggregate, such basic research will undoubtedly lead to more informative studies in humans and, hopefully, the ultimate elimination of hypoglycemia from the lives of people with diabetes.

The clinical problem is clear to millions of people with diabetes and, increasingly, to their caregivers: iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes (1, 2). It causes recurrent morbidity in most people with type 1 diabetes mellitus (T1DM) and many with T2DM and is sometimes fatal. The barrier