Renal AT2 Receptors in Ang II–Induced Hypertension (p 532)

**Activation of AT,R could be a novel therapy for hypertension, suggest Kemp et al.**

The renin-angiotensin system is an intricate network of hormones, enzymes and other factors that regulate sodium excretion and blood pressure. Angiotensin II (AT2), a key factor of the system, can either increase or decrease blood pressure depending upon the receptor with which it interacts. Interaction with AT,R, for example, induces vasoconstriction and decreases sodium excretion (natriuresis), resulting in an increase in blood pressure. While interaction with AT,R induces vasodilation and sodium retention. Because in most tissues the expression of AT,R is higher than AT,R the hypertensive effects of AT2 tend to predominate. Recently, a high-selective agonist of AT,R—compound 21 (C-21)—has been shown to boost AT 2R activation in rodents. Examining C-21 in more detail, Kemp and colleagues found that, in rats with experimental hypertension, C-21 significantly lowered blood pressure and raised natriuresis. Furthermore, the effects of C-21 were additive when it was combined with diuretics used to treat hypertension. The authors also found that C-21 promoted the cellular internalization of sodium transporters in the kidney, which could explain its natriuretic effects. Regardless of the mechanism, these results indicate that activation of AT,R could be an adjunctive therapy for hypertension.

Negative Regulation of Na+1.5 by the MAGUK CASK (p 544)

**CASK suppresses sodium channel expression in cardiomyocytes, report Eichel et al.**

Cardiomyocytes have well-organized membrane domains, such as the T-tubules, intercalated discs (ID) and lateral membranes (LM) that coordinate electrical and mechanical functions of these cells. These specialized domains differ in their compositions of ion channels, receptors and other cell-surface proteins. For example, the main cardiac sodium channel, Na+1.5—responsible for the rapid influx of Na+ ions (I Na) that initiates the action potential—is located both in IDs and LMs, but it interacts with different proteins at each site. From work on other cell types, it is known that members of the membrane- associated guanylate kinase (MAGUK) family organize surface proteins. Therefore, Eichel and colleagues investigated whether they might act similarly in the heart. They discovered that the MAGUK family member Calcium/CAlmodulin-dependent Serine Kinase (CASK) controls surface expression of Na+1.5 at the LM, but not ID. CASK directly interacted with Na+1.5 in rat cardiomyocytes and silencing CASK caused upregulation of Na+1.5 at LMs—and a resulting increase in I Na. The team went on to show that CASK— itself associated with the LM—exhibited reduced expression in cardiomyocytes from patients with atrial dilation, which suggests that the protein might be involved in pathological misregulation of Na+1.5 channels.

Arterial Disease and Progenitor Cells in CAD (p 564)

**Hayek et al link low numbers of blood progenitor cells with peripheral artery disease.**

Peripheral arterial disease (PAD)—shares many of the same risk factors as coronary artery disease (CAD), including older age, diabetes, smoking, hypertension and hyperlipidemia. However, it is unclear why some people develop PAD, others CAD, and others both. Patients with PAD have low levels of circulating mononuclear progenitor cells, which are thought to promote vascular repair and regeneration. Studies of progenitor cell levels in CAD patients, on the other hand, have given mixed results. Hayek and colleagues thus hypothesized that progenitor cell levels might be a distinguishing feature of PAD and CAD patients. They examined circulating progenitor cell numbers in 1497 CAD patients, 308 of whom also had PAD. Sure enough, they found that the patients with PAD and CAD had lower progenitor numbers than patients with CAD alone. Furthermore, low progenitor numbers were associated with an increased risk of myocardial infarction, death and PAD-related events within two years. Whether a decline in progenitor cell number precedes PAD is not known, but regardless the results suggest that low progenitor numbers could be a useful indicator of patients most at risk of adverse outcomes.
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