Renalase, a catecholamine-metabolizing hormone from the kidney

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Renalase, a catecholamine-metabolizing hormone from the kidney

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ABSTRACT | A novel flavin adenine dinucleotide-dependent amine oxidase that is secreted by the kidney, circulates in the blood, and modulates cardiac function and systemic blood pressure has recently been discovered. *Renalase* appears to be a hormone that metabolizes catecholamines, and its discovery will facilitate our understanding of sympathetic regulation.

It isn't every day that a new renal hormone is discovered. First, there was renin. Then came erythropoietin. The realization that the kidney is responsible for the final step in the production of active vitamin D led to the identification of a third hormone, calcitriol. The kidney also produces various prostaglandins and other products that may have substantial systemic effects.

Recently published work by Xu et al. employs a "tour de force" approach to give us a new renal hormone, "renalase" [6]. To find novel renal proteins, the authors applied a series of selection criteria to the complete collection of clones published by the Mammalian Gene Collection Project. First, they selected proteins with less than 20% sequence homology to known proteins. They also focused on proteins containing signal peptide sequences, which are key for protein export (of a hormone for instance). They excluded proteins that had transmembrane domains; the typical secreted protein lacks these. Next, Northern blot analysis was done for each of the 114 candidate genes thus identified. One clone (MGC12474) showed a robust preferential renal expression with lower expression in heart, skeletal muscle, and liver. The longest open reading frame encoded a novel protein of 342 amino acids that they termed renalase. In human kidney, renalase was present in the glomeruli and proximal tubules, while in the heart the enzyme was associated with cardiomyocytes.

The investigators generated a glutathione synthase-renalase recombinant protein in *E. coli* that they successfully purified. They observed that when flavin adenine dinucleotide (FAD) was omitted during protein synthesis, the synthetic renalase had no oxidase activity. Thus, renalase is FAD dependent. Renalase had a 13.2% amino acid identity with monoamine oxidase A (MAO-A), another FAD-dependent enzyme. MAO-A and MAO-B are mitochondrial outer membrane bound flavoproteins that catalyze the oxidative deamination of neurotransmitters and biogenic amines. A number of mechanism-based inhibitors have been developed for clinical use as antidepressants and as neuroprotective drugs. The three-dimensional crystal structure of MAO-B has been prepared; that for MAO-A should follow shortly. The amino acid identity of the two proteins is 70%.

The physiological function of MAO-A and MAO-B was elucidated by the study of Norrie disease. The three genes encoding NDP, MAO-A, and MAO-B lie adjacent to one another on the X chromosome. A contiguous chromosomal deletion of the three genes causes severe mental retardation, seizures, hypotonic crises, impaired somatic growth, and altered peripheral autonomic fucion. Loss of MAO-A and MAO-B is reflected neurochemically by severely reduced plasma and urinary concentrations of catecholamine-deaminated metabolites, including dihydroxyphenyl glycol, the deaminated metabolite of norepinephrine and epinephrine. An X-linked selective MAO-A deficiency has also been described, whose neurochemical phenotype closely resembles that in patients with the contiguous gene syndrome. The genes encoding MAO-A and MAO-B have also been deleted in the mouse [4]. MAO-A gene-deleted mice have increased circulating serotonin, norepinephrine, and dopamine, whereas MAO-B gene-deleted mice show increased phenylethylamine levels. Both MAO-detected strains were subjected to exogenous stress reaction tests and showed an increased response.

Based on the above information, the investigators pursued the notion that renalase might be important in amine oxidation. After identifying an amino-oxidase domain in the predicted amino acid sequence, a host of probable substrates were lined up for testing. Renalase gobbled up dopamine, epinephrine, and noreipnephrine in that order of preference. However, neither MAO-A nor MAO-B inhibitors (pargyline and clorgyline, respectively) could block renalase. The authors then purified renalase from human urine. The material again metabolized catecholamines with the same substrate specificity. Anti-renalase

antibody blocked the effects.

The authors then tested renalase in rats. Sprague-Dawley rats given intravenous renalase decreased their blood pressures by 25%; the effect dissipated within minutes. Heart rate decreased accordingly, as did cardiac contractility. The effects were dose dependent. The cardiovascular effects described by the authors were dramatic and convincing. The animals behaved as if they had been suddenly subjected to a massive α and β adrenoceptor blockade. As a matter of fact, such an experiment would have been a nice positive control.

Given these tantalizing basic findings, what is the evidence that a catecholamine-catabolizing enzyme produced in the kidney might be clinically relevant? Norepinephrine-containing renal sympathetic nerves innervate all segments of the kidney [2]. Neural regulation has a major effect on renal sodium and volume reabsorption, which in turn influences blood pressure. The tubular effects are independent of vasoconstriction. Neural activity also largely regulates renin release. There are three renal neuroeffectors: the vasculature, the juxtaglomerular granular cells, and the renal tubules. The renal neural regulation is modulated by renal afferent neural signals. However, the notion that the kidney might produce a hormone influencing catecholamines and their disposition was not anticipated.

Xu et al. [6] found that renalase is virtually absent in dialysis patients, although normal subjects have the material in abundance. Dialysis patients have increased sympathetic tone. Their circulating catecholamines are higher than nondialysis control subjects. Furthermore, sympathetic activity can be measured at the nerve level with microneurography in human subjects. The technique involves the placement of a very fine tungsten needle into the peroneal nerve, where the nerve wraps around the fibula at the knee. Dialysis patients are generally hypertensive and have increased sympathetic nerve traffic [1]. However, when bilateral nephrectomy is performed in dialysis patients, their hypertension generally goes away. Moreover, their muscle sympathetic nerve activity is reduced to normal or even lower levels. Conceivably, the increased sympathetic tone in dialysis patients is attributable to renalase deficiency. Nevertheless, the presence of diseased kidneys must also supply a signal since bilateral nephrectomy obviously cannot restore renalase.

The authors show that dopamine is effectively degraded by renalase. However, dopamine is associated with lower blood pressure and decreased cardiovascular risk. Felder et al. (2002) [3] found that in human essential hypertension, single-nucleotide polymorphisms of a G protein-coupled receptor kinase, GRK4γ, increased G protein-coupled receptor kinase (GRK) activity and caused serine phosphorylation and uncoupling of the dopamine D(1) receptor from its G protein/effector enzyme complex in the renal proximal tubule. The effect was verified in transfected Chinese hamster ovary cells. Their findings would suggest that diminished dopaminergic tone would increase blood pressure and cardiovascular risk. Renalase could have an adverse effect on blood pressure by lowering dopamine, particularly in the kidney.

There are distinct differences between MAO-A and renalase. Renalase is secreted into the circulation while MAO-A and MAO-B are confined to the intracellular mitochondrial membrane. The authors indicate that amine-oxidase activity has been measured in human plasma previously. The vascular adhesion protein 1 (VAP-1) is believed to mediate that activity. The VAP-1 protein is a copper-containing semicarbazide-sensitive amine oxidase that is secreted by vascular smooth muscle cells, adipocytes, and endothelial cells [5]. However, the substrate specificity of VAP-1 is very distinct from renalase.

The discovery of renalase will potentially contribute to our understanding of increased cardiovascular risk in patients with chronic renal disease. Cardiovascular risk correlates with sympathetic tone and circulating norepinephrine concentrations. Since renalase is made within the kidney, possibly its major function resides within the organ. Renal sympathetic nerve activity performs the fine-tuning of cardiovascular and blood pressure regulation. A potentially beneficial therapeutic effect for patients with hypertension or heart failure would be the blockade of α1-adrenergic receptors [2]. By metabolizing norepinephrine within the kidney, renalase could perform that function. The discovery of renalase will surely usher in a host of additional investigations into the mechanisms by which renalase may act and the role it plays. Most likely, the actions of renalase will be important to cardiovascular health in general and should extend far beyond patients with reduced renal function.

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