Regulating Renal Drug Elimination?

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Among the clinically highly relevant functions of the kidney is the elimination of xenobiotics, including drugs. In the past years a wide variety of transport systems have been identified serving renal transport of organic cations and anions (1–4). The operation of several of those transport proteins and the partially poor substrate selectivity allows the kidneys to efficiently eliminate a multitude of xenobiotics (1,3,4). Needless to say, altered function of the transporters is expected to modify plasma levels of the drugs and thus their efficacy and side effects. Nephrologists know well that acute or chronic renal failure affects the appropriate dosage of a wide variety of drugs (5). Compelling evidence suggests, however, that renal elimination of certain drugs could be compromised in a seemingly normal kidney.

In recent years polymorphisms of genes encoding proteins involved in the metabolism and subsequent renal and/or extrarenal elimination of xenobiotics have been shown to correlate with drug sensitivity (3,4). Gain of function of an organic cation transporter (OCT) relevant for drug elimination will decrease plasma levels and may prevent appropriate therapeutic effects at standard dosage. A loss-of-function polymorphism may lead to increased toxicity in affected individuals.

The article by Ciarimboli et al. (6) sheds new light on a further possible cause of deranged drug elimination, i.e., altered regulation of the carrier. The authors demonstrate that activation of protein kinase C (PKC) leads to strong stimulation of the organic cation transporter rOCT1 expressed in human embryonic kidney cells. In a laudable molecular analysis they identify the putative phosphorylation sites within the carrier molecule. Moreover, they provide evidence that PKC does not only increase the maximal transport rate but that it alters the relative selectivity of the carrier. Those observations could imply that the effect of PKC activation may not uniformly modify all substrates of the carrier. In prior studies (7,8) the authors provided evidence that cation transporter isoforms do not only differ in substrate affinities but also in regulation. The article in this issue of JASN is not only of high theoretical interest but may also disclose novel potential mechanisms causing deranged drug elimination.

First, stimulation of PKC and similar kinases may affect renal drug elimination. For instance, marked upregulation of PKC has been observed in diabetic nephropathy (9–16) which could in theory interfere with drug elimination. Moreover, gain-of-function or loss-of-function mutations of PKC related kinases may affect the regulation of the carriers and thus drug elimination. Polymorphisms of different PKC isoforms have been described and associated with diverse diseases (17–20). A common gain-of-function gene variant has been identified for the serum and glucocorticoid inducible kinase SGK1 (21), which is similarly upregulated in diabetic nephropathy (22) and regulates a wide variety of transport mechanisms (23,24). It would be interesting to explore whether any of those polymorphisms is associated with altered drug elimination. Finally, polymorphisms affecting the carrier phosphorylation sites may affect the in vivo regulation of the otherwise intact carrier and thus again modify drug excretion.

At this time, the role of dysregulated carriers in deranged drug excretion is a matter of speculation, and experimental efforts are required to explore the role of kinases in the excretion of xenobiotics. We are only beginning to appreciate that a seemingly normal kidney may differ in function and regulation of specific channels and carriers and that renal drug elimination may be sensitive to altered function or regulation of distinct carriers involved in the renal elimination of xenobiotics. Much has to be learned before the present knowledge can be translated into drug safety. But the article by Ciarimboli et al. (6) should encourage researchers to correlate polymorphisms of genes encoding transport-regulating kinases with drug elimination.

References

See related article, “Individual PKC-Phosphorylation Sites in Organic Cation Transporter 1 Determine Substrate Selectivity and Transport Regulation,” on pages 1562–1570.