Statins affect AQP2 traffic

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The aquaporin-2 water channel (AQP2) plays a critical role in mediating vasopressin action in the kidney collecting duct (4). Physiologically, vasopressin acts by activating the V$_2$ receptor on the basolateral side of these cells to trigger a classical G protein-coupled activation cascade resulting in increased cAMP and activation of protein kinase A (PKA). With the realization that AQP2 translocation from vesicles in the cytoplasm to the apical membrane increases apical water permeability (12, 13), studies then followed showing that PKA phosphorylation of the COOH terminal of AQP2 triggers the vesicular traffic that transfers AQP2 to the apical membrane in response to vasopressin (3, 5). A comprehensive review of this field has recently been published in the American Journal of Physiology-Renal Physiology (10).

But, like for most important physiological pathways, the list of factors affecting apical AQP2 levels has grown year by year with increasing complexity. The abundance of AQP2 in the apical membrane is affected by its rate of endocytosis as well as exocytosis (8, 11). Moreover, cAMP and PKA are not the only intracellular mechanisms involved. It was discovered that modulation of cGMP and PGE$_2$ pathways also impact AQP2 traffic (1, 2, 18).

Adding even further to this complexity are new observations indicating that the statins so widely used clinically to reduce cholesterol can also affect levels of AQP2 in the apical membrane. Initial studies examined long-term actions of statins and were believed to be due to statins’ established action of decreasing membrane cholesterol (14). A previous study had shown that levels of apical AQP2 channels are increased by cholesterol depletion because of reduced clathrin-mediated endocytosis of AQP2 (7). However, work by Li et al. (6) published in an issue of the American Journal of Physiology-Renal Physiology now shows that even acute exposure to simvastatin for times known to cause no significant changes in cholesterol can increase apical membrane AQP2 both in cultured cells and in Brattleboro rats, a strain that lacks any vasopressin.

The significance of these new findings extends beyond the identification of yet another pharmacological effect of statins. Intriguingly, the authors provide strong evidence that the effect on AQP2 traffic is due to simvastatin’s downregulation of RhoA activity, since overexpression of RhoA blocks elevation of AQP2 by simvastatin (6). Thus these studies add additional support to previous studies suggesting that statins have important effects on Rho GTPases (9, 16). Rho GTPases, in turn, appear to regulate the cytoskeleton and very likely endocytosis and vesicle trafficking (15, 17). Important details on exactly how Rho GTPases act to regulate AQP2 vesicle traffic are still unresolved. It also remains to be determined if there are similar effects of statins on endocytosis of other important kidney transporters or if AQP2 alone is affected. Nevertheless, this interesting new work strongly implicates RhoA in AQP2 regulation.

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REFERENCES