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REGULATION OF AQUAPORIN 2 FUNCTION

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Body fluid balance is controlled predominantly by hormonal regulation of renal collecting duct function. The water permeability of the collecting duct is controlled by vasopressin, which causes the shuttling of aquaporin 2 (AQP2) water channels from intracellular vesicles to the apical plasma membrane of the cells. This shuttling is mediated by cAMP and activation of protein kinase A: phosphorylation of AQP2 seems to be a key step leading to its exocytic insertion into the plasma membrane. When vasopressin levels fall, AQP2 is retrieved endocytically.

This acute shuttling of AQP2 is modulated by changes in AQP2 expression: vasopressin infusion, or chronic dehydration, increase AQP2 expression, while water loading decreases it. This modulation can be partly explained by vasopressin effects mediated by cAMP, but it is now clear that other factors are also involved. A number of other hormones and local factors are known to modulate antidiuresis, although in many cases the mechanisms behind this remain unclear. We have been particularly interested in possible roles of prostaglandins, angiotensin, and bradykinin. Prostaglandin E2 and angiotensin II both appear to have some ability to increase cAMP and hence mimic the effects of vasopressin, while bradykinin antagonises the effects of vasopressin. We are currently investigating the signalling cascades underlying these effects.

Pathological disorders of water balance have been shown to be associated with changes in both AQP2 expression and shuttling. In particular, many acquired forms of nephrogenic diabetes insipidus are associated with a decrease in AQP2 levels, which may be profound, while some, but not others, also show impaired trafficking of AQP2. In seeking treatments for such disorders, it is important to understand both why the disorder has arisen, and possible ways to bypass it. We hope that in the long term we can find stimuli that will alter both expression and shuttling of AQP2 independent of vasopressin, and that this will lead to new treatments for water balance disorders, and potentially for other problems such as hypertension.

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Where applicable, the experiments described here conform with Physiological Society ethical requirements.