Journal Club

NEUROENDOCRINOLOGY

FUNCTIONAL DIVERSITY OF CORTICOTROPIN-RELEASING HORMONE

In 1978, Wylie Vale and colleagues isolated corticotropin-releasing hormone (CRH) from sheep hypothalami and published a study of the modulation of stress-induced adrenocorticotropic hormone (ACTH) release by CRH. The study suggested that endogenous CRH has a physiological role in regulating ACTH secretion. In subsequent studies, the Vale team confirmed the peptide sequence of CRH, produced a CRH-specific antibody, identified central CRH receptors (and cloned the subtypes CRHR1 and CRHR2) and identified new family members of the urocortin family (1, 2 and 3). Since these publications, numerous fruitful findings from scientists around the world have supported the hypothesis that CRH from the hypothalamus, via the CRH receptors, controls every cell in the body in terms of maintenance and adaptive responses for homeostasis.

In 2003, Peter Agre (Nobel Laureate in Chemistry) discovered the water channel (aquaporin, AQP) and answered the question of how water crosses cell membranes. In 2014, Chen et al. showed that hypoxia (8% O_2 for 8 h) induces cerebral oedema and neuronal apoptosis, and also increases the expression of CRH, CRHR1 and AQP4 in the rat cortex. CRH, acting through CRHR1, triggers cAMP–PKA signalling and intracellular Ca^{2+} release; in addition, PKCε contributes to the phosphorylation and expression of AQP4 to enhance water influx into astrocytes. In 2020, Kitchen et al. found that the cell-surface abundance of AQP4 increases in response to hypoxia-induced (5% O_2 for 6 h) cell swelling in a calmodulin-dependent manner. Calmodulin binds to the AQP4 C-terminus, causing a specific conformational change and driving AQP4 cell-surface localization. In a rat model of spinal cord injury, inhibition of calmodulin with trifluoperazine inhibits AQP4 localization in astrocytes to the blood–spinal cord barrier, eliminates oedema in the central nervous system and accelerates functional recovery.

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In 2020, using magnetic resonance imaging, Mestre et al. revealed that entry of cerebral spinal fluid (CSF) into the brain along the glymphatic pathway is the principal mechanism of early oedema formation and ion perturbation during ischaemic stroke. They found that CSF flows into the brain after ischaemic stroke (middle cerebral artery occlusion (MCAO) for 15–60 min) and drives acute tissue swelling. The spreading ischaemia drives a rapid increase in perivascular CSF flow, and this spreading depends on AQP4 expression in astrocytes. Furthermore, AQP4-knockout mice do not develop oedema within the first 15 min after embolic MCAO. CRH and AQP will be targets for precision medicine; AQP as a sensor of cellular water balance and CRH as a sensor for whole-body homeostasis.

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Competing interests
The author declares no competing interests.

ORIGINAL ARTICLES Sutton, R. E., Koob, G. F., Le Moal, M., Rivier, J. & Vale, W. Corticotropin releasing factor produces behavioural activation in rats. *Nature* **297**, 331–333 (1982) | Rivier, C. & Vale, W. Modulation of stress-induced ACTH release by corticotropin-releasing factor, catecholamines and vasopressin. *Nature* **305**, 325–327 (1983) | Chen, S. J. et al. Overactivation of corticotropin-releasing factor receptor type 1 and aquaporin-4 by hypoxia induces cerebral edema. *Proc. Natl Acad. Sci. USA* **111**, 13199–13204 (2014) | Kitchen, P. et al. Targeting aquaporin-4 subcellular localization to treat central nervous system edema. *Cell* **181**, 784–799 (2020) | Mestre, H. et al. Cerebrospinal fluid influx drives acute ischemic tissue swelling. *Science* **367**, eaax7171 (2020)

IN BRIEF

DIABETES

Dexamethasone in patients with diabetes mellitus

Patients with COVID-19 who require supplemental oxygen and/or mechanical ventilation are routinely treated with dexamethasone. However, glucocorticoids can exacerbate dysglycaemia, and the benefits of dexamethasone treatment in patients with diabetes mellitus were unclear. A retrospective analysis has assessed data from the first two waves of the COVID-19 pandemic in the UK. Mortality was reduced in the second wave compared with the first wave, with dexamethasone being independently associated with reduced risk of admission to the intensive care unit and/or death. Furthermore, a multivariate analysis demonstrated that the independent effect size of dexamethasone was similar for patients with and without diabetes mellitus. The authors conclude that dexamethasone is beneficial for patients with severe COVID-19 and diabetes mellitus, but that treatment guidelines need to incorporate strategies to identify and manage steroid-induced hyperglycaemia.

ORIGINAL ARTICLE Eng, P. C. et al. The benefit of dexamethasone in patients with COVID-19 infection is preserved in patients with diabetes. *Diabetes Obes. Metab.* https://doi.org/10.1111/dom.14692 (2022)

DIABETES

HIF1α inhibition preserves β-cell function

New research has tested the hypothesis that the hypoxic phenotype of metabolic overload in type 2 diabetes mellitus is mediated by HIF1α. In db/db mice, treatment with PX-478, which inhibits HIF1α, prevented the rise in glycaemia and progression of diabetes mellitus. In streptozotocin-induced diabetic mice, PX-478 improved recovery of glucose homeostasis. The researchers isolated islets from these mice; these islets showed hallmarks of improved β-cell function, such as increased insulin content and formation of mature insulin granules. Human islet organoids that had been chronically exposed to high levels of glucose also responded positively to PX-478 treatment. The authors suggest that PX-478 could be an antidiabetic therapeutic agent that could be used to preserve β-cell function.

ORIGINAL ARTICLE Ilegems, E. et al. HIF-1α inhibitor PX-478 preserves pancreatic β cell function in diabetes. *Sci. Transl Med.* https://doi.org/10.1126/scitranslmed.aba9112 (2022)

METABOLISM

Urocortin 3 function in glucose metabolism

A new study has investigated the effects of urocortin 3 on glucose regulation in male rats. Subcutaneous administration of urocortin 3 resulted in inhibited gastric emptying and glucose absorption following oral administration of glucose. Urocortin 3 also inhibited insulin secretion, which meant that blood levels of glucose were similar for rats treated with a low dose of urocortin 3 and those treated with vehicle. A high dose of urocortin 3 resulted in increased glucose levels and lipolysis. In isolated rat small intestine, urocortin 3 infusion did not affect the secretion of incretin hormones. In isolated rat pancreas, urocortin 3 infusion increased secretion of somatostatin, and glucagon secretion was inhibited. The authors suggest that urocortin 3 is a glucoregulatory hormone, and that its mechanisms of action involve affecting pancreatic and gastrointestinal functions.

ORIGINAL ARTICLE Grunddal, K. V. et al. Opposing roles of the entero-pancreatic hormone urocortin-3 in glucose metabolism in rats. *Diabetologia* https://doi.org/10.1007/s00125-022-05675-9 (2022)