

## **Investigating the role of central nutrient-sensing neurones via adeno-associated viral manipulation of glucokinase**

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The classical picture of glucose homeostasis involves the liver, skeletal muscle and adipose tissue acting independently of one another under the control of the endocrine pancreas. However, evidence is mounting which suggests that glucose homeostasis is dependent on functional integration between tissue types under central control (1,2,3). Within the central nervous system, a sub-set of nutrient-sensing neurones (NSN's) have been identified in the ventromedial hypothalamus (4). Pharmacological inhibition of these neurones results in disruption of glucose homeostasis and energy balance (5). The exact function and mode of sensing of NSN's remains unclear. However, it is widely accepted that glucokinase (GK), which catalyzes the first reaction in glycolysis, plays a regulatory role. Manipulation of GK activity in the VMH, using adeno-associated virus (AAV), will help to elucidate both the manner in which these neurones sense nutrients and their physiological role.

In rats a twenty four hour fast or insulin induced hypoglycaemia resulted in increased GK activity, specific to the ARC, suggesting a central role of this region. To date the AAV constructs have been produced and tested *in vitro* and *in vivo*. In cultured cells, anti-sense GK-AAV knocks down GK activity by 38%, while sense GK-AAV increases GK activity by 217%. Expression studies have confirmed the efficacy of both constructs *in vivo*. Currently, the effects of AAV GK sense and anti-sense in the ARC are being investigated with regards to energy balance and glucose homeostasis. To our knowledge, these studies are the first physiological studies to chronically up and down regulate hypothalamic glucose sensing.

- 1) Lam et al 2005 *Nature Neuroscience* 8(5):579.
- 2) Lam et al 2005 *Nature Medicine* 11(3): 320.
- 3) Levin et al 1999 *Am J Physiol Regul Integr Comp Physiol*: 276.
- 4) Oomura et al 1964. *Science*: 484-485.
- 5) Berthoud and Mogenson 1977 *Am J. Physio* (233):127.