Glucose Sensing in the Brain

Seminar 2012

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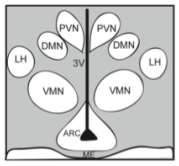
Brain

- Regulates energy homeostatis
  - acts in response to circulating signals of nutrient states
  - acts via the autonomic nervous system
- Ensures a balance between energy intake, expenditure and storage
  - --› maintaining body weight within tight limits

Autonomic Nervous System

- regulation of energy homeostatis is a coordinated effort between the **hypothalamus**, **amygdala**, **brainstem**, and others
- within the hypothalamus lies:

important! ▪ **ventromedial** VMH ⟶ ventromedial + accute nuclei
- ▪ **dorsomedial** DMH/DMN
- ▪ **lateral** LH
- ▪ **paraventrical** PVH/PVN



Exp Physiol 92.2 pp 311–319

Ventromedial Hypothalamus

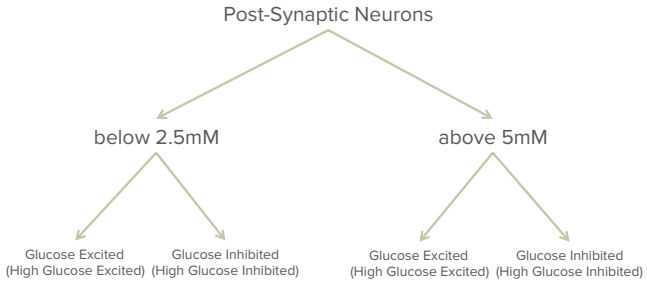
- contains two types of nuclei:
  - **ventromedial** (VMN)
  - **arcuate** (ARC)
- arcuate nuclei contains:
  - **neuropeptide Y** (NPY)
  - **pro-opiomelanocortin** (POMC)
- these have opposing effects on energy regulation
  - NPY increases food intake + activates energy sparing mechanisms
  - POMC decreases food intake + activates energy expenditute mechanisms

Hypothalamic Glucose Sensors

- theorised in 1950s by Jean Mayer
- report in 1986 by Campfield and Smith suggested glucose sensors regulate daily food intake (sensors in VMH and LH)
  - although recently disproved by Levin et al.
- Levin et al. found that decrease in VMH due to insulin-induced hypoglycaemia --› increase in food intake
  - consistent with important role of VMH in restoring euglycaemia (normal glucose levels)
  - further suggesting VMH sensors are important in detecting and countering severe glucose deficit

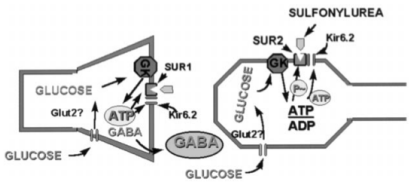
Glucose Sensing Neurons

- defined as “those which alter their action potential frequency in response to changes ininterstitial glucose levels”
- glucose can affect neurons either **pre**-synaptically (indirectly) or **post**-synaptically (directly)
- there are two types of post-synaptic neurons:
  1. those which respond to increases above 5mM
  2. those which respond to increases below 2.5mM
- these classes can both be split into Glucose-**excited** and Glucose-**inhibited** neurons



Subclasses of Post-Synaptic Glucose Sensing Neurons

GE + GI respond to changes between 0.1 and 2.5mM
HGE + HGI respond to changes between 5 and 20mM



GE Neuron

also called “Glucose Responsive”

Hypothetical model of ATP-sensitive K^+ channel (KATP) complex on glucose-responsive (GR) neurons. Neuronal cell bodies may contain a glucose transporter (possibly GLUT-2) and/or a hexokinase [possibly glucokinase (GK)], which regulates entrance of glucose into cell and rate of glycolysis, respectively, at physiological concentrations found in brain. Hexokinase is located in plasma membrane close to KATP channel. Channel is composed of a low-affinity sulfonylurea receptor (SUR2) and Kir6.2 pore-forming unit. This arrangement provides relatively high ratios of ATP to ADP at the channel during glycolysis. Binding of ATP inactivates channel, whereas phosphorylation increase its activity. At axon terminals of GABA, glutamate, or other transmitter neurons, KATP channel consists of a high-affinity SUR (SUR1) and Kir6.2 pore-forming unit. Either binding to channel of ATP derived from glycolysis or occupation of SUR would inactivate channel, leading to increased firing of neuron or transmitter release at terminal.

GE Neurons

- found in ARC and VMN
- uses ATP sensitive potassium (K_{ATP}) channels to sense glucose
  - like pancreatic β cells
- concentration-response relationships for both channel currents and action potential frequency reveal steep and linear relationship between glucose concentration and neuronal activity between 0.1 and 1.5mM glucose
- curve then decreases sharply and plateaus at 2.5mM and 5mM glucose.
- suggests role in sensing and detection of enery deficit within physiological parameters

GE Neurons

- other similar characteristics with beta cells:
  - GLUT2 (glucose transporter) and GK (glucokinase) are expressed in **both** cells
    - half of VMH GE neurons express GK
    - 30% express GLUT2
    - 50% express GLUT4
  - $\Delta\alpha_2$.AMPK KO mice also lack ARC GE neurons
- **suggests multiple subtypes of GE neurons that use different glucose sensing mechanisms**

GE Neurons and ARC POMCs

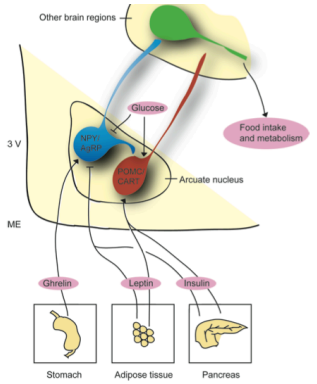
- studies suggest GE neurons belong to ARC POMC population
  - electrical activity of POMC neurons ∞ energy status
- Ibrahim et al and Claret et al have demonstrated this using GFP labelled POMC promoter
- **this is still controversial**

VL-VMN

- located between the ARC and the VMN regions along the ventrolateral border of the VMN
  - VL-VMN
- VL-VMN believed to be heavily involved in metabolism regulation
  - VL-VMN lesioned mice ⇢ obese
- Neurotoxin goldthioglucose (causes T2DM) destroys neurons in VL-VMN
- poorly researched due to lack of markers and por understanding of neuronal circuitry

GE Neurons (again)

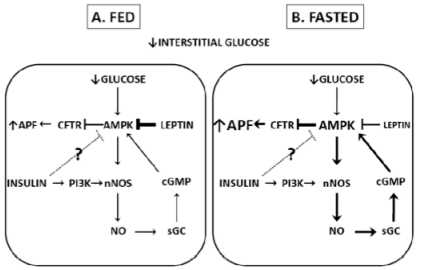
- other than being located in VL-VMN, they also respond to peripheral adiposity signals such as leptin, insulin
  - POMC activated by leptin/insulin
  - NPY inhibited
- Spanswick et al showed insulin has profound inhibitory effect of GE neurons via K_{ATP} channel activation
  - however not at 2.5mM glucose
    - suggests physiological environment can regulate GE sensitivity to regulatory signals
    - when glucose is low there is an increased need to respond, while at higher levels the need is decreased
- Spanswick also showed leptin in 10mM glucose causes complete GE inhibition through K_{ATP} activation (through PI3K signalling pathway)
  - although at 2.5mM some neurons are inhibited, excited or have no response, suggesting only some neurons have leptin receptors
  - → **multiple subtypes of GE neurons!**



Hypothalamic Feeding Centres

GI Neurons

- in some respects very similar to GE neurons
  - GLUT2/4, GK expressed
- **however,** the signal transduction pathway which changes in intracellular ATP alter activity is completely different
- **AMPK** is an important protein which is activated when glucose decreases and is targetted by a number of homones and transmitters which regulate energy balance



Signalling pathway in GI neurons

detail on next slide

Detail

- activated AMPK phosphorylates neuronal NO synthase (nNOS) --> NO production
  - nNOS is the target of many hormones, such as insulin and leptin (act via PI3K pathway)
- ↑NO → stimulation of soluble guanylyl cyclase → ↑cGMP → ↑AMPK activation
  - amplication required to depolarise GI neuron in low glucose
  - leads to activation of kinases and effector molecules such as CAMKK

Sensitivity of sensors

- in normal energy status, glucose sensing neurons do not respond to small changes in interstitial glucose
  - leptin (↑ in energy sufficient state) blocks AMPK and ↓ sensitivity
- in diabetes, neurons become ↑sensitive

Counterregulation Response (CRR)

- to prevent deleterious effects of **hyper**glycemia in diabetics (esp. T1DM), intensive insulin therapy is used
- however this often leads to **hypo**glycemia
- under normal circumstances, powerful neuroendocrine and autonomic CRR prevent and correct hypoglycemic conditions
  - CRR involves the release of glucagon, epinephrine and corticosterone
  - if CRR occurs too many times, hypoglycemia-associated autonomic failure (HAAF) results

T2DM

- Type 2 Diabetes Mellitus (T2DM) is associated with insulin and leptin resistance
- both hormones prevent VMH GE and GI, respectively, from sensing glucose deficit
- in T2DM individuals, the VMG glucose sensing neurons are **inappropriately responsive** to glucose deficits

T2DM

- there is a causal evidence for GE neurons in the development of T2DM and obesity
- hypersensitisation of glucose sensing neurons would lead the brain to believe that an energy *deficit* existed in the presence of energy *sufficiency* or *excess*
- inappropriate signal of energy deficit would result --› obesity

T2DM

- there are also *in vivo* studies that suggest VMH GI neurons may be more sensitive to glucose decreases in T2DM and obese individuals

References

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- Routh, V. H. (2010). **Glucose sensing neurons in the ventromedial hypothalamus** *Sensors (Basel, Switzerland)*, *10*(10), 9002–9025. doi: 10.3390/s101009002
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