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## SUMMARY

Low blood sugar, or hypoglycaemia, is detected by specialised sugar sensing neurons in the brain. However, detection of hypoglycaemia is blunted after repeated hypoglycaemia and this is due to adaptive mechanisms kicking in within the brain, mechanisms that resemble the 'training effect' in muscle. These adaptations most likely increase the tolerance of the brain to stress, but also perturb the detection of hypoglycaemia, further increasing the likelihood of hypoglycaemia.

## Hypoglycaemia: Exercise for the Brain?

Most of us, unless we engage in extreme endurance sports, will never experience low blood sugar, or hypoglycaemia. This is because glucose is an essential fuel and is extremely tightly regulated. This is fortunate as hypoglycaemic episodes, apart from reducing energy supply, are also unpleasant experiences characterised by a marked symptom response (e.g. sweating, palpitations, tremor, nausea), affecting cognition and mood in a negative way. Research has shown that specialised regions of the brain monitor blood glucose levels, which if reduced below the normal range initiate a counterregulatory defence response. This primarily involves activation of the autonomic nervous system (sympathetic nerve activation and release of catecholamines, adrenaline and noradrenaline) with an additional stimulus of pancreatic alpha-cell glucagon release (which acts on the liver to increase glucose production and release into the circulation).

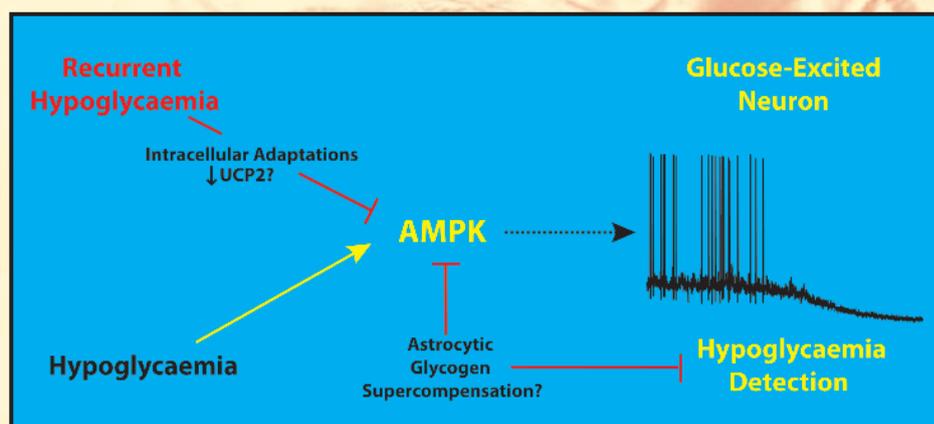
Type 1 diabetes results from autoimmune destruction of pancreatic beta-cells causing

insulin deficiency and can be fatal if untreated with insulin. In type 1 diabetes hypoglycaemia occurs frequently, in some cases every other day. The reasons for this are complex and the focus of considerable research but we know that people with type 1 diabetes have profound defects in normal hypoglycaemia counterregulatory mechanisms. Understanding the mechanisms of hypoglycaemia detection and why they fail in type 1 diabetes is essential if we are to develop treatments to prevent hypoglycaemia. Interestingly, recent work indicates an important role for an energy sensor originally discovered in muscle cells.

### Energy sensor

Energy stress, such as that associated with muscle contraction during exercise results in increased activity of the enzyme AMP-activated protein kinase (AMPK). When activated this enzyme activates a set of responses that adapts muscle for future exercise. In other words,

Mechanisms of AMPK regulation within the ventromedial hypothalamus in response to hypoglycaemia.



exercise-induced AMPK activation is critical for the training effect in muscle. These adaptive changes ensure that to continually improve fitness, you must work harder to engage these adaptive mechanisms. Could this adaptation be responsible for the reduced ability to detect hypoglycaemia seen in type 1 diabetes? AMPK is present in the brain and crucially within glucose-sensing regions such as the ventromedial hypothalamus (VMH). The VMH contains neurons that act indirectly to modify glucagon and adrenaline secretion and so control their outputs during hypoglycaemia. Importantly, hypothalamic AMPK is activated by low glucose. Furthermore direct pharmacological activation of hypothalamic AMPK amplifies the counterregulatory response to hypoglycaemia. Conversely, genetic repression of hypothalamic AMPK prevents the normal electrical response of glucose-sensing neurons to low glucose and suppresses the counterregulatory response. Clearly AMPK is important in hypoglycaemia detection and regulation of whole body glucose counterregulation.

### Brain training

Most people with diabetes do not undergo a single isolated episode of hypoglycaemia. Troublingly, an increasing frequency of hypoglycaemic episodes increases the risk of further and more profound hypoglycaemia. This also occurs experimentally using rodent models, which respond in a very similar fashion to humans. Thus recurrent hypoglycaemia (3 bouts of up to 2 hours) is sufficient to suppress the counterregulatory response, even in non-diabetic rodents. The same is true for non-diabetic humans following only one exposure to clinically controlled hypoglycaemia. It appears as though adaptive mechanisms underlie this

response, i.e. the brain prepares itself for future energy stress. Possibly, activation of AMPK associated with hypothalamic-limited hypoglycaemia is delayed after recurrent hypoglycaemia.

Interestingly, the electrical responsiveness to glucose of a sub-group of glucose-sensing neurons is reduced by recurrent hypoglycaemia. Thus glucose levels must drop further before these neurons respond to the hypoglycaemic stimulus.

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*“the brain prepares itself for future energy stress”*

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This can be viewed as analogous to the training response in muscle, where exercise must reach a higher intensity before adaptive responses kick in. This raises the questions as to whether recurrent hypoglycaemia is “training” for the brain in response to future energy stress i.e a normal adaptation to stress that maladaptive to the function of critically important glucose-sensing neurons. Frequent hypoglycaemia was a stress not experienced by our ancestors, where prolonged starvation was the norm rather than multiple rapid onset short-term hypoglycaemia exposures.

### Mechanisms of brain training

To develop potential treatments we need to identify the molecular events that underpin normal glucose-sensing behaviour, where they occur and how these are modified by recurrent hypoglycaemia. Indeed, evidence

from targeted knockout of AMPK in glucose-sensing  $\beta$ -cells has shown that uncoupling protein 2 (UCP2) is down-regulated. UCP2 provides a means for dissipating excess energy, so reduction in UCP2 should enhance cellular energy levels. However, it is highly likely that additional molecules also contribute to glucose-sensing and these may be modified by recurrent hypoglycaemia. Indeed, muscle exercise physiology can provide clues. For example, glycogen “supercompensation” occurs in trained muscle and this acts as an intracellular fuel source for prolonged exercise. Glycogen is also found in the brain, in specialised support cells called astrocytes. Indeed, brain glycogen levels are increased following recurrent hypoglycaemia, further supporting the idea that “training” adaptations occur.

We anticipate further investigation into these mechanisms will pave the way to new therapeutic targets to restore the counterregulatory response in diabetes.

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