

# Fuel sensing and the central nervous system (CNS): implications for the regulation of energy balance and the treatment for obesity

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## Summary

This review describes the product of the 3-day International Association for the Study of Obesity (IASO) Stock Conference held in March 2004 and sponsored by Abbott Laboratories. The conference was focused on how the mechanisms by which individual cells sense their own fuel status might influence the energy balance of the entire organism. Whether you are a single-celled organism or a sophisticated mammal with a large cerebral cortex, it is critical that cellular activity be matched to the available fuel necessary for that activity. Rapid progress has been made in the last decade in our understanding of the critical metabolic events that cells monitor to accomplish this critical task. More recent developments have begun to apply this understanding to how critical populations of neurones may monitor similar events to control both food intake and energy expenditure. The picture that emerges is that numerous peripheral fuel sensors communicate to the central nervous system (CNS) via neural and humoral routes. Moreover, it has been known for decades that specific populations of neurones sense changes in ambient glucose levels and adjust their firing rate in response and changes in neuronal glucose metabolism can influence energy balance. The CNS, however, does not just sense glucose but rather appears to be sensitive to a wide range of metabolic perturbations associated with fuel availability. This information is used to adjust both caloric intake and the disposition of fuels in the periphery. Increased understanding of these CNS fuel-sensing mechanisms may lead to novel therapeutic targets for obesity.

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The accurate matching of caloric intake to caloric expenditure involves a complex interplay among a number of organ systems. Part of this regulation involves the monitoring of stored fuel, most of which is in the form of triacylglycerol accumulated in adipose tissue. The discovery of leptin and continued advances in understanding the neural systems upon which leptin acts have dramatically increased our knowledge about how adipose mass is sensed. Moreover, we also understand a great deal about how our bodies mediate the responses to negative or positive energy balance by altering both food intake and energy expenditure.

While little doubt can be cast that such monitoring of stored fuel is a critical aspect of energy balance regulation, organisms must not only assure themselves that they have sufficient calorie stores but also assure that they have sufficient available fuel to meet their immediate metabolic needs. These ‘fuel-sensing’ mechanisms have evolved to meet the need of the organism to assure all cells have adequate fuel to carry out their ongoing functions. What should be obvious, however, is that just as the signals from stored fuel must impact on how fuel is being acquired from the environment and how it is being utilized by various tissues, signals from fuel sensors must also be able to

impact both feeding behaviour and the physiological processes that free up and expend fuel sources. As such the ongoing regulation of energy balance must integrate signals about the status of stored fuel as well as immediate fuel availability. In order to advance our knowledge of the fuel-sensing side of this equation, International Association for the Study of Obesity (IASO) organized the third annual Stock conference that brought together 23 scientists (see Table 1) with a wide range of backgrounds that related to fuel-sensing mechanisms in a variety of species and systems. This conference series, generously supported by Abbott Laboratories Inc., honours Michael Stock, an enormously energetic researcher whose scientific career was cut short by cancer. This article is a summary of the 3 days of work by these 23 individuals.

The metabolic problem for individual cells is clear. They need to be able to adjust their most energy demanding tasks to the amount of fuel available to them. In the case of yeast, their major job is to grow and multiply. In nutrient-rich environments, they must be able to rapidly divide and grow so as not to be crowded out by other competitors within that nutrient-rich environment. To that end, these single cell organisms have developed highly tuned fuel-sensing mechanisms that sense energy status in multiple ways. Intracellular phosphorylation of protein kinase A (PKA) is associated with energy surfeit and periods of rapid growth (1). The phosphorylation of PKA is controlled by a number of inputs that reflect the energy status both inside and outside of the yeast (2). Most interestingly, however, yeast appear to have homologues to mammalian glucose and

amino acid transporters that are incapable of actually transporting nutrients. Rather than transporting nutrients, these molecules appear to detect the presence of nutrients outside the cell and signal to intracellular regulatory systems. Their signalling allows yeast growth and metabolic machinery to be stimulated very rapidly even before nutrients are processed inside the cell. Very little is known about whether such extracellular nutrient detectors are widely distributed in mammalian tissues.

In mammalian cells ribosomal protein synthesis is the most energy demanding activity and must be curtailed in situations where sufficient energy is not available. The energy status of all mammalian cells involves a number of critical proteins that are linked to protein synthesis. Among these is the mammalian Target of Rapamycin (mTOR), which integrates insulin signalling with cellular fuel status (3). Sufficient activity of mTOR and its downstream effectors such as S6 Kinase 1 are required for normal protein synthesis (4). Further, mTOR activity seems to be directly influenced by ATP concentration within a cell (5). Thus the activity of mTOR is carefully regulated by a cellular fuel status and in turn regulates adenosine monophosphate (AMP)-activated kinase to influence an enormous number of energy consuming cellular processes. The rapidly advancing work around mTOR and its downstream targets is an excellent example of the progress being made in understanding how individual cells sense their fuel status.

While all cells need to regulate their individual protein synthesis, mammals must sense a variety of specific aspects of fuel availability. As a result, they have specialized cell

**Table 1** Participants in the 2004 Stock Conference on central nervous system (CNS) fuel sensing

Antonio Del Parigi	National Institute of Health, Phoenix, AZ, USA
Joel Elmquist	Beth Israel Deaconess Medical Center, Boston, MA, USA
Deborah Good	University of Massachusetts, Amherst, MA, USA
Joanne Harrold	Department of Medicine, Liverpool, United Kingdom
Akio Inui	Kobe University Graduate School of Medicine, Japan
Annette Kirchgessner	GlaxoSmithKline, Harlow, United Kingdom
Wolfgang Langhans	Swiss Federal Institute of Technology, Switzerland
Charles Mobbs	Mount Sinai School of Medicine, New York, NY, USA
Tim Moran	John Hopkins University School of Medicine, Baltimore, MD, USA
Margaret Morris	University of Melbourne, Victoria, Australia
Chris Morrison	Pennington Biomedical Research Center: Louisiana State University System, Baton Rouge, LA, USA
Naima Moustaid-Moussa	University of Tennessee, Knoxville, TN, USA
Christopher Newgard	Sarah Stedman Nutrition and Metabolism Center, Durham, NC, USA
Silvana Obici	Albert Einstein College of Medicine, Bronx, NY, USA
Sue Ritter	Washington State University, Pullman, WA, USA
Gabriele Ronnett	John Hopkins University School of Medicine, Baltimore, MD, USA
Vanessa Routh	New Jersey Medical School, Newark, NJ, USA
Amanda Sainsbury Salis	Garvan Institute of Medical Research, Darlinghurst, Australia
Randy Seeley	University of Cincinnati, Cincinnati, OH, USA
Johan Thevelein	Katholieke Universiteit Leuven, Leuven-Heverlee, Belgium
George Thomas	Friedrich Miescher Institute, Basel, Switzerland
Joerg-Peter Voigt	Freie Universität Berlin, Institute for Pharmacology and Toxicology, Berlin, Germany
David A. York	Pennington Biomedical Research Center: Louisiana State University System, Baton Rouge, LA, USA

types that have developed highly specific fuel-sensing mechanisms for a particular purpose. For example, pancreatic  $\beta$ -cells must be able to detect glucose to appropriately regulate insulin secretion. A great deal of work points to that secretion being controlled by intracellular metabolic processes that include but are not limited to glucose (6). A critical feature of type II diabetes is associated with impairment of the ability of  $\beta$ -cells to respond sufficiently to increased glucose levels. An important question is how this reduced capacity to respond to glucose occurs. Recent work has shown that insulin secreting cell lines show profound differences in their capacity to respond to extracellular glucose. Using nuclear magnetic resonance (NMR)-based analysis of glucose metabolism, the degree to which glucose can stimulate 'pyruvate cycling' has been shown to correspond to the glucose-stimulated insulin response in each cell line (7). Pyruvate cycling refers to the process whereby pyruvate carboxylase acts on pyruvate to produce oxaloacetate that can in turn be reduced to malate. Malate can then be returned to pyruvate via the actions of malic enzyme. The higher the activity of this cycle, the greater is the glucose-stimulated insulin secretion.

An important question is whether impairment of pyruvate cycling is associated with conditions that reduce glucose-stimulated insulin secretion. Exposure of insulin secreting cell lines to high levels of fatty acids results in lipid laden islets with reduced glucose-stimulated insulin secretion. Exposure of these impaired cells to adenoviruses encoding malonyl-CoA-desaturase results in increased lipid oxidation and reduced lipid levels. However, this treatment is not sufficient to restore normal insulin secretion. Fatty acid exposure also results in reduced pyruvate cycling and the application of a pyruvate cycling intermediate, dimethyl malate, results in increased pyruvate cycling and completely restores the ability of these cells to respond to increased glucose with robust insulin secretion (8). These data support the hypothesis that it is not lipid accumulation *per se* that impairs these cells but rather the impairment of activity within a specific metabolic pathway. Such findings exemplify the progress that is being made in the fuel-sensing pathways of peripheral cells. Critical future questions centre around whether neurones monitor similar metabolic outputs to determine their activity as they regulate the organism's food intake and energy expenditure.

Other peripheral cell types with the ability to communicate directly to the central nervous system (CNS) also appear to have fuel-sensing capabilities. One such cell type is the ghrelin producing cells found primarily in the stomach and to a lesser extent in the intestine (9). Ghrelin secretion is influenced by both individual meals and overall energy balance. Decreased body fat stores are associated with increased levels of circulating ghrelin and ghrelin levels increase prior to individual scheduled meals (9). Thus it would appear that ghrelin producing cells are sensing a

number of things about the status of energy in the periphery and a great deal of work is focused on what specific factors influence ghrelin secretion. Some reports have shown that exogenous ghrelin can produce increased food intake and increased gene expression for specific orexigenic neuropeptides such as neuropeptide Y and agouti-related protein. A great deal of controversy remains about the importance of ghrelin in the control of energy intake and overall energy balance regulation. The secretion pattern of ghrelin, however, makes it a potential mechanism by which peripheral fuel status can be communicated to the CNS.

The liver is another peripheral organ that appears to carefully sense levels of available fuel and communicate that information to the CNS to regulate food intake and energy expenditure. In many ways, the liver is ideally situated to sense peripheral metabolic events given its essential role in regulating levels of nearly all essential fuels. Co-infusion of insulin and glucose into the major blood supply of the liver (the hepatic portal vein) can reduce meal size (10). Similarly, lactate can also produce reductions in food intake (11). Evidence also links hepatic lipid oxidation to the control of food intake as well. Infusion of agents that decrease fatty acid oxidation in the liver can cause increased food intake (12). Given that both glucose and lipid changes within the liver appear to be associated with the control of food intake, some investigators have posited that ATP generation or concentration within hepatocytes constitute an important signal (13). Infusions of the fructose analogue 2-5-AM or manipulations of hepatic membrane potential result in decreased ATP levels and increased food intake (14). All of these hepatic signals appear to depend critically upon vagal afferents because cutting the hepatic vagus or treatment with capsaicin blocks the ability of these liver manipulations to alter food intake.

The importance of this liver signal is revealed by experiments involving rats made diabetic by administration of streptozotocin. When maintained on standard high-carbohydrate diets, rats become dramatically hyperphagic as their diabetes develops and more and more fuel is lost via the urine. However, when animals are placed on diets high in fat, calorie intake returns to levels identical to the amount consumed prior to the streptozotocin treatment and this normalization of intake is associated with the normalization of mRNA levels for several critical hypothalamic neuropeptides (15). This is remarkable given the levels of leptin remain exceptionally low. Cutting the vagal nerves which innervate the liver blocks the ability of high-fat diets to reverse this diabetic hyperphagia (16). Thus a critical hepatic signal can powerfully regulate food intake and hypothalamic neuropeptide gene expression even in the face of very low levels of stored fuel and circulating leptin.

Vagal afferents have been implicated in both the effects of fuel-sensitive gut peptides (CCK, ghrelin, GLP-1) and hepatic signals known to regulate food intake. Other

aspects of the peripheral nervous system also appear to sense cellular fuel status. The enteric nervous system coordinates activities in much of the viscera and some enteric neurones appear to have glucose-sensing properties similar to that of pancreatic  $\beta$ -cells (17). Enteric neurones express some of the same machinery as  $\beta$ -cells including glucokinase and subunits of  $K_{ATP}$  channels. Importantly, enteric neuronal firing rate is altered by ambient glucose levels. Interestingly, like the ghrelin secreting cells from the stomach, some of these neurones secrete orexin that also has the ability to increase food intake via actions in the CNS (18,19). These data make a good case for neuronal fuel sensing that occurs in the enteric nervous system that likely helps regulate gastric motility.

Key to the regulation of energy balance is the CNS that guides the control of both food intake and energy expenditure. The primary fuel for neurones is glucose and consequently decades of research have focused on the ability of neurones to sense ambient glucose and transduce this signal into changes in activity that regulate food intake (20,21). The most compelling evidence for this comes from the direct application of various analogues of glucose that are taken up by neurones but inhibit glucose oxidation. These analogues can produce robust increases in food intake while simultaneously increasing available glucose from the plasma (22). While it makes a great deal of sense that the CNS would protect itself from glucoprivation under extreme circumstances, proving that these effects contribute to day-to-day regulation of food intake has been more difficult.

One powerful piece of evidence for a role for a key role for glucose sensing in the CNS comes from electrophysiological recordings of *ex vivo* neuronal slices. Specific subsets of neurones alter their firing rate based on ambient glucose levels (20,21). Under most physiological conditions, glucose fluctuations in the CNS are relatively small. Regardless, many of these neurones appear to change their firing rate in response to changes of glucose that fall within the narrow range observed in the CNS. Such glucose-sensing cells are found in regions associated with the control of food intake such as the ventromedial and arcuate nuclei of the hypothalamus as well as the nucleus of the solitary tract in the caudal brainstem.

Interestingly, the response of these specialized neurones is not unidirectional. One subset of these neurones increase their firing rate in response to increased levels of glucose and are therefore termed 'glucose-stimulated' neurones. Another set decrease their firing rates in response to increased levels of glucose and are therefore termed 'glucose-inhibited' neurones. Even within a specific subregion such as the arcuate nucleus, both types of neurones can be identified. The ability of select populations of neurones to respond differentially to physiological changes in glucose make a strong case for them having a specific purpose. One

logical purpose for such neurones is that they are involved in the control of nutrient intake. Consistent with this hypothesis, glucose sensitive neurones within the arcuate have their firing rate influenced by other signals known to influence food intake such as insulin and leptin (23).

While historically glucose sensing has received the lion share of the attention concerning fuels and their impact on the CNS, a growing body of evidence in recent years supports the notion that specialized neurones are paying attention to more than glucose. Among the first of the findings to indicate that other fuels and metabolic pathways may be critical to the regulation of food intake was the finding that inhibitors of fatty acid synthase (FAS) can potently inhibit food intake (24). In lipogenic tissues such as adipose or liver, FAS catalyses malonyl-CoA into fatty acids so that they can be stored. However, several lines of evidence point to the direct actions of FAS inhibitors in the CNS to suppress food intake (25,26). Why should the CNS that runs almost entirely on glucose be influenced by the levels of FAS? One potential answer is that specialized sets of neurones are paying attention to a wide variety of fuels that extend beyond glucose.

Consistent with this hypothesis are recent data showing that infusions of oleic but not palmitic acid result in suppressions of food intake and decreased glucose output from the liver (27,28). Long-chain acyl CoAs enter mitochondria via carnitine palmitoyltransferase-1 (CPT-1). Recent data demonstrate that both FAS and CPT-1 are found in neurones including neurones within the arcuate nucleus (29). Moreover, CNS reductions in CPT-1 expression or activity results in potent decreases in food intake and decreased glucose output from the liver (30). Thus despite the dogma that neurones do not utilize fatty acids for energy, convincing evidence points to a critical role for both fatty acid production and utilization in regulating CNS circuits that regulate food intake.

A number of competing hypotheses have been proposed as to the critical signalling events inside neurones that mediate the effects of these unusual CNS metabolic events that can influence food intake. One common feature of these three manipulations (infusion of oleic acid, inhibition of CPT-1 or inhibition of FAS) is that all would be predicted to result in increased intracellular long-chain acyl CoA concentrations. Consequently one hypothesis is that long-chain CoAs in the cytoplasm of neurones have signalling properties that can influence either activity or gene expression within critical populations of neurones in the hypothalamus (27). Consistent with this hypothesis, recent data has shown that different metabolic conditions can result in altered levels of long-chain acyl CoAs in whole hypothalamus. An alternative hypothesis is that all of these manipulations result in changes in glucose uptake or utilization within neurones and that it is these resulting glucose changes that alter neuronal activity (31). This would make

it possible to unite the well-described glucose-sensing mechanisms of select neurones with the manipulations of fatty acid production or utilization. Data consistent with this hypothesis take advantage of the fact that in the presence of ketones, neurones will stop utilizing glucose and preferentially oxidize ketones. If alterations in glucose uptake and/or utilization are critical events, then manipulations such as FAS inhibition should be ineffective in rats maintained on a diet that causes ketosis. In fact, FAS inhibitors are unable to suppress food intake in rats on a ketogenic diet (31). Moreover, when co-infused with other glucose metabolites that will reduce glucose uptake by neurones such as glutamine or lactate, C75 is also less able to suppress food intake. Such data point to a role for glucose uptake into neurones as important to the actions of FAS inhibition. Whether this is also true for infusion of oleic acid or CPT-1 inhibition is not known.

A third hypothesis involves the cellular fuel sensor AMP-activated kinase. A large body of research points to this kinase as an important part of the response of a wide variety of cell types to alterations in both glucose and lipid fuel availability (32). AMP-activated kinase activity is increased in response to low levels of cellular fuels. Recent studies show that levels of AMP-activated kinase are increased in the CNS during negative energy balance and decreased by leptin. Further, reduced activity of AMP-activated kinase in the hypothalamus reduces food intake and body weight (33). Finally, FAS inhibition results in decreased AMP-activated kinase activity and the effect of C75 to reduce food intake can be blocked by pharmacological increase in AMP-activated kinase activity (34).

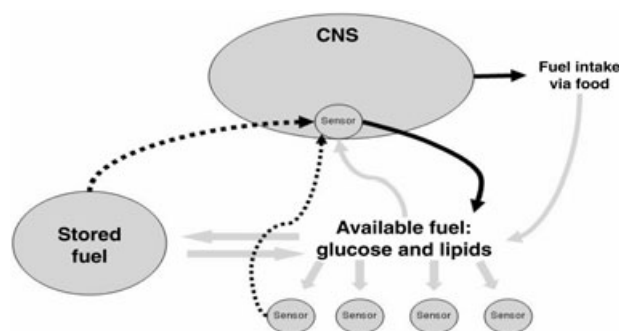
Ultimately, these hypotheses are not mutually exclusive and all of these events may contribute to the ability of these non-glucose manipulations to alter food intake. Answering the degree to which these potential mechanisms represent parallel or serial actions that connect alterations in fuel status to alterations in activity and gene expression of specific populations of neurones remains a vital question. While great progress has been made in peripheral cell types, answering these questions in the CNS is far more difficult. If this kind of overall fuel sensing is going on in the CNS, it may not be occurring in the vast majority of neurones. Rather, it may be limited to a small number of specialized neurones located in the hypothalamus and caudal brainstem. Thus, our ability to identify, measure and manipulate the specific neurones involved in this process is quite limited.

Further, much of the progress in understanding these metabolic signalling pathways has come from the aggressive use of immortalized cell lines. While neuronal cell lines exist it is simply not clear whether they will model the special properties of neurones involved in cellular fuel sensing. After all, our bodies have gone to great lengths to protect neurones from being exposed to vagaries in avail-

able fuel because they have only small intracellular stores and cannot typically be replaced. To make them effective fuel sensors, they must be exposed to the shifting fuel mix and availability that occurs in the periphery. As a consequence, it is possible that not all neurones would have the needed properties and it is simply not clear whether neuronal cell lines have the specialized properties of a neuronal fuel sensor. This makes it difficult because it prevents the easy application of advanced NMR technologies that can measure activity in specific metabolic pathways. Finally, it is not the case that all of the fuel sensing actually has to occur within the neurone itself. Rather, associated glia may play an active role in sensing fuel and in turn alter the activity of neurones by altering the fuels they provide to neurones.

## Conclusion

The picture that emerges from this burgeoning field is one in which fuel sensing occurs in a number of peripheral cell types (see Fig. 1). Each of them is reading their cellular fuel status and at least some of these cell types can produce neural or humoral signals that act on the CNS to impact energy balance. In addition to these numerous peripheral fuel sensors, specialized neurones within the CNS also directly sense their own fuel status. Clear evidence links levels of glucose to ongoing activity of critical populations of neurones that likely participate in the regulation of energy balance as well. Further, a growing spectrum of data indicate that, like many peripheral cell types, some neurones integrate information on fuel sources other than glucose to impact both food intake and peripheral fuel levels. Finally, growing evidence links these sensors of cellular fuel status to the key signals of stored energy in adipose tissue like leptin. Thus a critical question is to identify the mechanisms by which signals of stored and available fuel are integrated in the CNS. This integrated information is then used to not only guide choices the animal makes about how many fuels to take in from the environment but also how



**Figure 1** Theoretical model of ongoing fuel sensing by the central nervous system (CNS) and its influence on food intake and peripheral fuel utilization.

stored fuels should be distributed and metabolized by various peripheral tissues.

A related question is whether this new information about the mechanisms through which the CNS is sensing fuel will result in novel therapeutic approaches to treat obesity. One strategy could be to activate these neuronal fuel sensors to indicate that there is plenty of available fuel. This would result in reduced caloric intake and increased caloric expenditure. This could potentially be accomplished with pharmacological agents directed at the signalling cascades associated with these fuel sensors. Further understanding of these CNS fuel-sensing mechanisms is likely to yield additional targets for such pharmacological intervention. Alternatively, it may be possible to design nutrient analogues that could be ingested with food that would provide little in the way of oxidizable fuel for peripheral cells but would be still keep fuel-sensing mechanisms reading 'full'.

The difficulty of either of these strategies should not be underestimated however. It is logical that these CNS cellular fuel-sensing mechanisms are similar to their peripheral counterparts. Thus, it will be difficult to find mechanisms to increase the fuel-sensing mechanisms in the CNS that will not result in similar effects on peripheral tissues. For example, when CNS cellular fuel sensors read that fuel is abundant it may produce the desired effect of reduced food intake. However, in muscle cells that same fuel sensor reading 'full' may result in an undesired effect of insulin resistance as the muscle avoids taking up further nutrients. Consequently, titrating the peripheral and central effects of these manipulations would be crucial to achieve the appropriate balance that would maximize the benefits while minimizing any potential harmful side effects. Regardless of the obstacles to using these CNS cellular fuel sensors in treatment, it has become clear that they play a crucial role in the overall regulation of energy balance and therefore will receive additional research attention in the coming years.

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