physiological function has been unclear. We have now shown that it is a regulatory domain and that binding of glycogen to it causes allosteric inhibition of AMPK. Glycogen is a polymer of glucose units joined by α1-4 linkages, with occasional branches formed by α1-6 linkages. A major problem with the study of glycogen as a regulatory molecule is that it does not have a defined structure, but varies both in size and branching content. Based on findings suggesting that the degree of branching affected its inhibitory potency, we have synthesized small α1-4 linked glucose oligosaccharides containing single α1-6 branches, and have shown that these are potent allosteric inhibitors of AMPK. The most potent oligosaccharide gives half-maximal inhibition at 90 μM, and also markedly inhibits phosphorylation of Thr-172 by LKB1 and CaMKKβ. Inhibition is due to binding to the GBD, because point mutations in the latter than abolish glycogen binding also abolish inhibition.

One of the physiological targets of AMPK is muscle glycogen synthase (mGS), which is inactivated by phosphorylation at Ser-7 [4]. A curious paradox is that although AMPK is activated by ATP depletion during exercise, mGS is usually found to be dephosphorylated and activated following exercise, as long as the exercise had been sufficiently prolonged to cause significant glycogen depletion. We believe that the regulation of AMPK via the GBD may explain this paradox. The outer tier of glycogen (representing the glucose that can be released by glycogen phosphorylase without the need for the action of debranching enzyme) contains up to one third of all of the glucose units in a single molecule. Theoretical studies suggest that in a fully synthesized molecule of glycogen the outer chains are so tightly packed that the branch points would not be accessible. We suspect that under these conditions AMPK binds to glycogen but is not inhibited, so that it would phosphorylate mGS, thus exerting a feedback inhibition of further extension of the outer chains of glycogen. We also propose that when exercise commences, phosphorylase removes some of the outer chains, exposing the branch points which would then bind AMPK and cause inhibition. mGS would now be dephosphorylated and activated by the glycogen-bound forms of protein phosphatase-1, so that it was ready to replenish glycogen stores as soon as exercise ceased. This hypothesis may also explain why insulin-stimulated glucose uptake and glycogen synthesis is enhanced following a single bout of exercise, as long as the exercise bout was sufficient to cause significant glycogen depletion. It can also answer another unsolved question: how do cells "know" when their glycogen stores are sufficient, and conversely how do they "know" when they are insufficient and need replenishing? These are important questions because insulin resistance, the primary cause of type 2 diabetes and the metabolic syndrome, can be viewed as a mechanism to limit the amount of nutrient that cells can store.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA11

The carotid body; a chemosensitive neurogenic center

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The carotid body (CB), a small neural crest-derived paired organ located at the carotid bifurcation, is a principal component of the homeostatic acute oxygen (O_2) sensing system required to activate the brainstem respiratory center to produce hyperventilation during hypoxemia (e.g. in high altitude residents or in patients with chronic obstructive pulmonary diseases) (Weir *et al. 2005*). The CB parenchyma is organized in glomeruli, clusters of cells in close contact with a profuse network of capillaries and afferent sensory fibers joining the glossopharyngeal nerve. The most abundant cell types in the CB glomeruli are the neuron-like, glomus or type I cells, which are enveloped by processes of glia-like, sustentacular type II cells. Glomus cells are physiologically complex, as they are electrically excitable and express a broad variety of voltage- and ligand-gated ion channels, as well as TRP and background K^+ channels. These cells behave as presynaptic-like elements that establish contact with the postsynaptic sensory nerve fibers.

Glomus cells are arterial chemoreceptors, activated by hypoxia, hypercapnia and extracellular acidosis. Recently, it has been shown that, as suggested by experiments *in vivo* (Alvarez-Buylla & Alvarez-Buylla, 1988; Koyama *et al*. 2000), glomus cells *in vitro* are glucose sensors, releasing transmitters in response to hypoglycemia (Pardal & Lopez-Barneo, 2002; Garcia-Fernandez *et al*. 2007). Hypoxia and hypoglycemia are additive stimuli that appear to activate cell secretion through separate pathways converging on cell depolarization and extracellular Ca^{2+} influx. Responsiveness to hypoxia seems to depend on inhibition of voltage-gated K^+ channels (Weir *et al*. 2005), whereas sensitivity to hypoglycemia depends on activation of a non-selective cationic conductance (Garcia-Fernandez *et al*. 2007).

Besides its sensitivity to acute hypoxia, the CB also exhibits a well-known adaptive hypertrophic response to chronic hypoxemia, whose underlying mechanisms are poorly known. We have investigated whether adult CB growth in chronic hypoxia is due to the activation of a population of resident stem cells. Exposure of mice to a hypoxic (10% O_2 tension) isobaric atmosphere for three weeks induced a marked CB enlargement (~2-3 fold) caused by dilation and multiplication of blood vessels as well as expansion of the parenchyma, with increased number of tyrosine hydroxylase positive glomus cell clusters. Although some glomus cells can enter a mitotic cycle in

response to hypoxia, the *de novo* production of CB glomus cells mainly depends on a population of stem cells, which form multipotent and self-renewing colonies *in vitro*. Cell fate mapping experiments *in vivo* indicate that, unexpectedly, CB stem cells are the glia-like sustentacular cells (Pardal *et al*. 2007). CB stem cells can be identified using glial markers such as the glial fibrillary acidic protein. Quite remarkably, the newly formed glomus cells have the same complex chemosensory properties as mature glomus cells in situ. They contain voltage-gated Ca^{2+} and K^+ channels, are highly dopaminergic, and secrete neurotransmitters on exposure to acute hypoxia and hypoglycemia. These cells are also producers of glial cell line-derived neurotrophic factor (Pardal *et al*. 2007). Induction of CB growth in sustained hypoxia seems to depend, at least in part, on factors possibly produced by glomus cells and the neighbouring vascular tissue.

These observations suggest that CB glomus cells are polymodal chemoreceptors with an important role in oxygen and glucose homeostasis. They also indicate that the mammalian CB is a neurogenic niche with a recognizable physiological function in adult life. CB stem cells may explain the origin of some tumours in humans (e.g. paragangliomas) and they could also be potentially useful for antiparkinsonian cell therapy.

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SA12

Matching ventilation to systemic metabolism: a role for peripheral chemoreceptors?

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Elevations in systemic metabolism brought about by exercise will raise the venous partial pressure of CO_2 and decrease venous Po_2 and pH. Despite these changes in venous blood composition, steady state arterial blood gas tensions and pH are retained at normal, 'resting' levels by a proportional increase in alveolar ventilation, thus demonstrating the sensitivity and functional importance of the respiratory system to changes in blood chemistry. The means by which metabolic rate is 'sensed' to initiate the appropriate hyperpnoea is, however, not known with certainty and a number of mechanisms have been implicated. These include both neural and humoural mechanisms, implicate both feedforward and feedback mechanisms and even include the possibility that exercise hyperpnoea is a learnt phenomenon. Additionally, a degree of redundancy may occur in the system with each proposed mechanism apparently able to account for most, if not all, of the ventilatory responses observed.

We have raised metabolic rate in anaesthetised rats by means of insulin infusion and have shown that such a manoeuvre can raise ventilation without alteration in arterial blood gas tensions via alteration in carotid body CO_2[1,2]. In the absence of carotid bodies, elevations in metabolic rate led to excessively high falls in blood pH. Additional experiments we performed on in vitro carotid body preparations showed that this organ was not sensitive to a fall in glucose concentration and afferent chemodischarge was not elevated, but could even be decreased by severe hypoglycaemia. We subsequently suggested that circulating adrenaline might act to augment rat carotid body sensitivity and other studies have revealed that a number of other hormones may account for the response seen in humans[3]. Elevations in ventilation and CO_2 sensitivity may be observed even with the relatively small increase in post-prandial metabolism. However, in contrast, to our findings, there are other reports to show that the rat carotid body has an *in vitro* sensitivity to falls in glucose concentration and it has been suggested that it may act as a peripheral glucosensor[4], although the mechanism for sensing glucose appears to involve carotid body type 1 cell membrane channel activation rather than the inactivation known to occur during hypoxia. The reasons for the discrepancies are not known, but it has been suggested that an interaction between Po_2 and glucose may be important[5] or that the particular preparation used can influence the findings.

Whilst evidence to date regarding some role for the carotid body in mediating exercise hyperpnoea appears strong, more studies are warranted to establish precisely how metabolism is sensed so precisely.

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SA13

ATP-sensitive potassium channels and neonatal diabetes: a treatable channelopathy

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ATP-sensitive potassium (K_{ATP}) channels are metabolic sensors that couple the metabolic state of the cell to the electrical activity of the plasma membrane. They consist of pore-forming Kir6.2 and regulatory sulphonylurea receptor (SUR) subunits. Metabolic regulation of channel activity is mediated by changes