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Some thoughts on the importance of insulin in the regulation of the blood glucose level

E. A. Newsholme[a] and G. Dimitriadis[b]

[a]*Cellular Nutrition Research Group, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU (England), Fax +44 1865 275 259*
[b]*Athens University, Department of Medicine, 103–105 Aegeou Pelagous Str., GR-153 42 Agia Paraskevi (Greece)*

Abstract. Insulin can influence rates of glucose utilization by muscle and possibly other tissues via both direct and indirect effects. It can control the rate of fatty acid mobilization from adipose tissue and the rate of fatty acid oxidation in muscle, and the latter inhibits glucose utilization and oxidation. Insulin may influence the levels of insulin-like growth factors I and II, both of which have effects on rates of glucose utilization by muscle. The inter-tissue cycle between glucose and lactate – the Cori cycle, which is influenced by insulin – may provide another novel mechanism for control of blood glucose. How far other anti-insulin hormones affect these processes is not clear.
Key words. Insulin; fatty acids; insulin-like growth factors; Cori cycle.

Introduction

The isolation of insulin in 1921 and the marked effect of its injection into diabetic patients on their blood glucose level led not only to an emphasis, perhaps an over-emphasis, on its effect on carbohydrate metabolism, but also focused attention on this one hormone in relation to control of the blood glucose level. From general knowledge of biochemical control processes it would be expected that, if insulin lowers the blood glucose level, other hormones should be present that will increase the level. Thus a balance between concentrations of insulin and of 'anti-insulin' hormones and the responses of tissues to both insulin and 'anti-insulin' hormones would be expected, from general principles, to regulate the blood glucose level within the normal narrow range. Imbalances in the level of hormones, could therefore lead to hypoglycaemia (excess of insulin or deficiency of 'anti-insulin' hormones) or to hyperglycaemia (insulin deficiency or excess of 'anti-insulin' hormones). It is known that anti-insulin or 'counteregulatory' hormones exist: they include growth hormone, catecholamines, glucagon and glucocorticoids. However, an important question is how these influence or indeed control the blood glucose level. Three speculative suggestions are made below.

The importance of lipolysis in adipose tissue in control of the blood glucose level

The major store of triacylglycerol in the body is in adipose tissue but it is mobilized in the form of long chain fatty acids, which are carried to other tissues via the bloodstream. Hence some tissues, for example muscle, oxidize fatty acids derived from adipose tissue to provide energy, and this is important in conditions such as starvation, prolonged exercise and stress[17]. However, the oxidation of fatty acids is more important than just the provision of energy.

The concept of the glucose/fatty acid cycle, put forward by Randle et al.[20], provides a mechanism by which fatty acid oxidation decreases the rate of glucose utilization and particularly glucose oxidation by muscle and possibly by other tissues[16]. There is now considerable evidence to support the important proposal that, under conditions of 'carbohydrate stress' (defined here as when the glycogen store in the liver is reduced), fatty acids are mobilized from adipose tissue, their rate of oxidation by muscle increases and this, in turn, decreases the rate of glucose utilization and oxidation (see, for example ref. 2). Conversely, when the carbohydrate stress is removed (e.g. by refeeding after starvation) the rate of fatty acid release by adipose tissue is decreased, their rate of oxidation by muscle is decreased, so that the rate of glucose utilization by the muscle (and other tissues) increases. And this is controlled, at least in part, by the increase in the concentration of insulin after feeding, since insulin inhibits the lipase in adipose tissue; indeed it is one of the few agents that can inhibit lipolysis[17].

An important point, however, is that insulin can affect the rate of fatty acid oxidation in muscle by a more direct means – via an increase in the level of malonyl-CoA. The latter is an inhibitor of the key enzyme in fatty acid oxidation, carnitine palmitoyl transferase[7,8]. Hence, insulin can affect the rate of fatty acid oxidation by two means, a direct effect on muscle and a direct effect on adipose tissue. Unfortunately, the balance between the effects of insulin on the rate of lipolysis and on that of fatty acid oxidation is not known.

The advent of the concept of the glucose/fatty acid regulatory cycle in the 1960s enabled a new interpretation of how insulin regulates the blood glucose level to put forward: increase in the insulin concentration de-

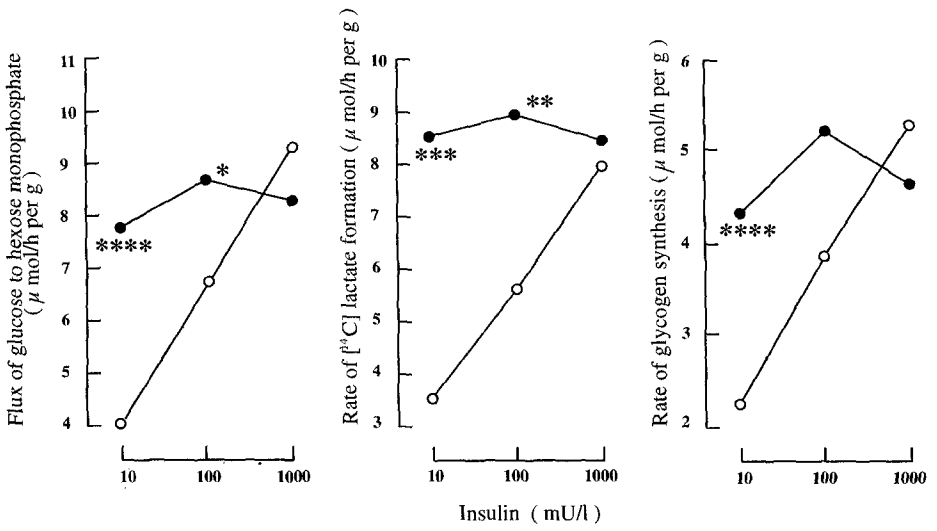

Figure. Effects of in vivo administration of IGF-I on the flux of glucose to hexose monophosphate and on the rates of [^{14}C]lactate formation and glycogen synthesis in soleus muscles isolated from rats ($n = 10$) 1 hour after IGF-I (●) or saline (○) injection. The soleus muscle strips were incubated in vitro with various concentrations of insulin. Results are presented as means ±SE of at least four separate incubations. *P < 0.05, **P < 0.02, ***P < 0.005 and ****P < 0.001 compared with control (*non-paired Student's t-test*).

creases the rate of fatty acid oxidation in muscle, and this effect results in an increased rate of glucose utilization by muscle. It is possible that anti-insulin hormones will also influence glucose utilization via effects on adipose tissue lipolysis and/or the control of the rate of fatty acid oxidation by muscle.

Insulin-like growth factors

Recently, studies have been carried out on the effects of insulin-like growth factor I (IGF-I) on the rates of glucose transport and utilization of glucose in the isolated soleus muscle; the results show that the effects of IGF-I are complementary to those of insulin[6, 6a]. Thus, IGF-I may be as important a regulator of glucose utilization by muscle as insulin; it could provide for *local* regulation of the uptake of glucose by individual muscles or groups of muscles since it can be produced by endothelial cells, and its rate of production and release could, therefore, be regulated locally. The in vitro experiments show that IGF-I is able to mimic the effects of insulin on carbohydrate metabolism in muscle and this will appear as an apparent increase in insulin sensitivity (fig.). It is tempting to speculate that the effects of IGF-I to increase the rate of glucose metabolism in muscle may be more important than those of insulin and that the major effect of insulin in vivo is its anti-lipolytic effect! If insulin could influence the local level of IGF-I in tissues or influence the free level of IGF-I via a change in the concentration of a binding protein(s) for the IGFs, the resulting change in the latter might influence glucose utilization by muscle to a much greater extent than could be produced by normal physiological changes in the plasma insulin level.

In addition it is interesting that, at least in muscle in vitro, IGF-I does not increase the rate of glucose oxidation but has a preferential effect on increasing the rate of lactate formation[6]. Since this lactate is transported to the liver where it will be converted to glucose via gluconeogenesis, this means that IGF-I may increase the activity of the Cori cycle.

It has recently been shown that IGF-II at physiological concentrations increases the sensitivity of glucose utilization and glycogen synthesis to insulin in the isolated soleus muscle[1]. This raises the intriguing question as to whether changes in insulin sensitivity caused by such conditions as exercise, chronic treatment with catecholamines or even adenosine[19], could be caused by local changes in the concentration of IGF-II. Such a change could influence the rate of glucose uptake by muscle without any need for a change in the plasma level of insulin.

Anti-insulin hormones and the Cori cycle

The above discussion raises the question of whether failure to control the blood glucose level in diabetic patients is caused mainly by changes in the level or the effectiveness of insulin. Anti-insulin hormones could exert a greater than expected effect in diabetic patients to cause an increase in the plasma glucose level. The history of work on anti-insulin hormones suggests this is possible.

Even before the isolation of insulin in 1921, there were many indications that carbohydrate metabolism could be influenced by other hormones. The glands antagonistic to the pancreas were thought to be the pituitary, the thyroid and the adrenals. In the earlier part of this century, the importance of the anterior lobe of the

pituitary in relation to glucose metabolism was discovered: the following facts were established[9]:

1) In pancreatectomized dogs, hyperglycaemia was lower and glycosuria did not occur if the dogs were hypophysectomized; however, subcutaneous implantation of the anterior lobe of the pituitary re-established the severity of diabetes. In a more recent study in diabetic dogs, hypophysectomy resulted in a general improvement of the diabetic state[11].

2) Injection of an anterior hypophyseal extract caused resistance to the effects of insulin and its hypoglycaemic effects. Houssay[9] has reported that daily intraperitoneal injections of anterior pituitary extract into dogs produced a rise in blood glucose on the second or third day, which reached a level of 8.3–16.7 mM in the fasting state.

3) Hypophysectomized animals have increased sensitivity to insulin[9] but this was abolished by administration of purified growth hormone[4].

4) Hypophysectomized animals easily become hypoglycaemic and rapidly deplete their hepatic glycogen store during fasting; this can be prevented by giving anterior lobe extract which was considered to contain a 'glycostatic factor' (this 'factor' was subsequently found to be growth hormone).

In addition to the pituitary, the involvement of other endocrine glands in the regulation of glucose metabolism was examined. For example, thyroidectomy was found to increase the ability of dogs to use intravenous glucose and to decrease the glycosuria which followed pancreatectomy. On the other hand, the administration of thyroid hormone to partially depancreatized dogs was found to produce diabetes.

These and other observations established the possible involvement of other endocrine glands in the pathogenesis of diabetes mellitus. As stated by Houssay in 1942: "Diabetes is a disturbance in the endocrine equilibrium between the secretion of insulin on one hand and the secretion of the anterior hypophysis, adrenals and thyroid on the other"[9].

It is well known that insulin resistance is important in the pathogenesis of type II diabetes. Insulin resistance is defined as a subnormal response of the glucose level to a given concentration of insulin. It could be caused by defects intrinsic to the insulin target cells or by factors that affect the response of the target cells to insulin. Thus, high rates of secretion of glucocorticoids, growth hormone, glucagon or catecholamines in endocrinopathies, infection or stress can induce insulin resistance; they may also be involved in type II diabetes[16].

The question arises as to whether there is a general mechanism by which the anti-insulin hormones and insulin could influence control of the blood glucose level and if this mechanism would still operate even when both insulin and the anti-insulin hormones were no longer present. A speculative proposal is that this general mechanism involves the Cori cycle (see below).

Glucose transport and glycolysis. It has been known since 1950 that insulin increases the rate of transport of glucose across the cell membrane in both muscle and adipose tissue so that this process has, for many years, been a focus of attention. It is now known that insulin increases the number of glucose transporters (GLUT-4) in the plasma membrane, probably by increasing the rate of translocation of the GLUT-4 transporter from an intracellular membrane store to the cell membrane in both adipose tissue and in skeletal muscle[4,12]. However, there are a number of important questions and points of discussion that are raised by this effect, which could influence, perhaps dramatically, our understanding of the physiological role of insulin. An important point is that, in muscle and adipose tissue, the glucose transport process is non-equilibrium so that it can respond to the influence of insulin. (In contrast, in liver, the process is near equilibrium, so there would be no point for this process to be stimulated by insulin. The control of the rate and direction of glucose flux in the liver therefore shifts to the enzymes glucokinase and glucose 6-phosphatase[17].) In a normal, physically active animal that eats only enough food for maintenance, insulin may control the rate of glucose utilization primarily through its effects on glucose transport and glycogen synthesis in muscle. In this way, glycogen that had been used by the muscle during exercise would be replaced after the meal. It is well established that, after prolonged exercise, glycogen replacement occurs in the muscle before it occurs in the liver[10], and indeed, glycogen is synthesized in muscle after exercise even during a period of starvation, when liver glycogen would be broken down[14]. It is possible to propose, therefore, that glycogen synthesis in the liver depends upon control of glucose metabolism in muscle (see above). This indeed, may be the *raison d'être* for the *indirect pathway* for glycogen synthesis in liver (that is, that some/most of the glycogen that is synthesized in the liver after a meal is derived not so much from glucose but from lactate, alanine and other gluconeogenic processors; see ref. 17 for an accurate historical account of this topic). Hence, when the amount of food ingested is above that required for replacement of muscle glycogen, it is suggested that insulin controls the blood glucose level by increasing the rate of transport of glucose into muscle but this then increases the rate of glycolysis in muscle so that more lactate is formed and released into the bloodstream. This will then, via glyconeogenesis, cause replacement of the glycogen store in the liver by the indirect pathway.

The conversion of glucose to lactate in muscle and the conversion of lactate to glycogen in liver may be part of an inter-organ communication system designed to provide precision in regulation. The conversion in muscle controls the blood level of glucose, an excess of which can be dangerous, and the increase in the blood lactate concentration, together with an increased hep-

atic blood flow, will facilitate the conversion of lactate to glycogen in the liver. Thus it is interesting to consider that the stimulation by insulin of the rate of glucose transport in muscle via a feed-forward regulation from digestion and absorption of carbohydrate in the intestine, may lead directly, but via a long and complex inter-tissue metabolic pathway, to increased levels of liver glycogen.

The normal blood lactate concentration (about 1 mM) represents a steady-state concentration that reflects the balance between the rates of production and utilization. Most of the lactate that is removed by the liver is converted to glucose or glycogen, via gluconeogenesis. The conversion of lactate to glucose in the liver and the continuous formation of lactate from glucose in the other tissues of the body represents a cyclical flow of carbon that has been termed the Cori cycle (after Carl Cori, who originally put forward the idea). It may have greater physiological significance than just that of a carbon link between peripheral tissues and the liver (see below).

In injury, burns, surgery or other stress, the plasma levels of growth hormone, glucocorticoids and thyroxine may increase. These changes will lead to an increase in the plasma levels of gluconeogenic precursors, which together with increased levels of hormones such as glucagon will increase the rate of gluconeogenesis, and the process probably results in the production of glucose rather than glycogen. The glucose which is produced will return to the blood and be available as a fuel for white blood cells and for cells involved in repair[18]. Therefore, under these conditions it is important that muscle (which is a major tissue of glucose utilization) does not use and in particular does not oxidize the glucose; this may be accomplished via the increased rate of fatty acid oxidation and the glucose/fatty acid cycle. Thus, most if not all of the glucose entering muscle is converted to lactate. The advantage of these changes is to increase the level of lactate in blood and therefore to induce an increase in the rate of the Cori cycle.

By maintaining a high flux through the Cori cycle, a dynamic buffer of key metabolic intermediates is provided both in the tissues and in the bloodstream, so that intermediates are available to cells whenever they are required. If the rate of glucose utilization by essential tissues such as brain and white cells is low in comparison to the flux through the Cori cycle, this is equivalent to a high cycling/flux ratio and could provide for precision in regulation of glucose utilization by these cells[19]. This may be one reason for an increased Cori cycle flux in hyperthyroidism when, although there is generalized resistance to insulin, muscle may convert glucose to lactate at a higher rate than normal[5]. The 'physiological' insulin resistance may be important in allowing a greater activity of the Cori cycle, as occurs in various conditions in which the body is subject to 'nutritional' stress. It may also be important during injury, sepsis, or after surgery or burns, when although there is generalized resistance to insulin, muscle may also have a higher rate of conversion of glucose to lactate[13].

It is interesting to consider that type II diabetes may be seen as a 'false stress' condition; that is, there is development of insulin resistance in muscle, an increase in the plasma levels of anti-insulin hormones, and an increase in the activity of the Cori cycle. The increased Cori cycle activity may be caused by at least some of the anti-insulin hormones. A decrease in the plasma levels of anti-insulin hormones would therefore be expected to ameliorate the diabetes but there would be a decrease in the sensitivity of tissues to the utilization of glucose, via the Cori cycle. Hence, if the glycogen stores are seriously depleted, hypoglycaemia could readily occur. And, as shown by Houssay, in hypophysectomized animals, although blood glucose concentration remains constant, if large demands for glucose occur (such as if the animals are stressed or starved), then the control mechanisms cannot adapt and hypoglycaemia results[9]. Thus, the decrease in blood glucose levels observed by Houssay after a decrease in the plasma levels of anti-insulin hormones in diabetic animals could be explained by a decrease in the plasma level of fatty acids and a decrease in the activity of the Cori cycle. These mechanisms could suggest some new approaches to treatment of patients with type II diabetes: a decrease in the rate of fatty acid oxidation by muscle or fatty acid release from adipose tissue, an increased rate of conversion of lactate to glycogen rather than to glucose in the liver, or an increase in the sensitivity of muscle to insulin, possibly by changes in the concentration of local hormones such as IGF-I and IGF-II. Indeed, the therapeutic administration of IGF-I has already been tried in patients with type II diabetes, with promising results[21].

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