

Nonrespiratory effects

β -Agonists and metabolism

L. H. Philipson, MD, PhD *Chicago, Ill*

This review presents recent concepts of how β -agonists affect glucose homeostasis by modulating insulin secretion, liver metabolism, and uptake of glucose into muscle, with attention to the influence of hypoglycemia on β -agonist sensitivity and the effects of β_3 -adrenergic receptor (β_3 AR) polymorphisms on adipocyte metabolism. Specific β_2 -agonist effects on the pancreatic β cell result in increased insulin secretion, yet other mechanisms, such as increased glucagon secretion and hepatic effects, cause an overall increase in serum glucose and an apparent decrease in insulin sensitivity. Human studies confirm the presence of β_2 ARs on pancreatic β cells. Intensive treatment of diabetes mellitus with insulin, especially in type 1 diabetes, has led to increased incidence of hypoglycemia. Repeated episodes of hypoglycemia lead to unawareness of neuroglycopenia, a major limitation to intensive treatment. Hypoglycemic unawareness is associated with reduced β -agonist sensitivity. Scrupulous avoidance of hypoglycemia over many weeks to months can restore β -agonist sensitivity and improve detection of hypoglycemia. β -agonists have also been employed to prevent hypoglycemia. β -agonists can increase thermogenesis and lipolysis, leading to increased energy expenditure and decreased fat stores. While β_1 ARs and β_2 ARs mediate many of these actions, it is likely that β_3 ARs in the adipocyte membrane also play an important role. Specific β_3 AR subtypes have been associated with obesity and the metabolic syndrome. (*J Allergy Clin Immunol* 2002;110:S313-7.)

Key words: β -agonist, glucose metabolism, insulin secretion, hypoglycemia unawareness, adipocyte metabolism

β_2 -adrenergic receptor (β_2 AR) agonists primarily exert their clinical effects in the lung, but multiple tissues and cell types clearly have functional and physiologically relevant β_2 ARs. This review presents recent concepts of how β -agonists can affect glucose homeostasis by modulating insulin secretion, liver metabolism, and uptake of glucose into muscle, with attention to how hypoglycemia affects β -agonist sensitivity and how β_3 AR polymorphisms affect adipocyte metabolism.

INTEGRATED EFFECTS OF β -AGONISTS ON GLUCOSE HOMEOSTASIS

Clearly there are risks to using β -agonists.¹ The effects

Abbreviations used

ATP: Adenosine triphosphate
 β_2 AR: β_2 -adrenergic receptor
 β_3 AR: β_3 -adrenergic receptor
 $[Ca^{2+}]_i$: Intracellular calcium
cAMP: Cyclic adenosine monophosphate

relative to metabolism do not seem to be a major problem in most clinical situations, but multiple studies with β -agonists show a tendency to hyperglycemia in intact animal models or humans. Given that many patients with asthma or chronic obstructive pulmonary disease are also given glucocorticoids, and may be sedentary and overweight, a small rise in fasting blood glucose may be significant. By using the current standard of diagnosis of a fasting blood sugar ≥ 126 mg/dL, an increase in the fasting blood sugar of even 1 to 2 mg/dL (18-36 mmol/L) may be enough to bring a patient into the classification of diabetes mellitus.

Because β -agonists are frequently given during labor, there has been interest in the effects on insulin secretion and glucose metabolism in pregnant women. In one of the earliest such studies, hexoprenaline, a β_2 -sympathomimetic drug, was shown to cause first a detectable increase in insulin concentration within 10 minutes, followed by an increase in glucose concentration in 30 minutes.² Plasma glucagon and free fatty acid levels also increased, despite the increase in glucose concentrations,² leading the authors to conclude that the β_2 -agonist had direct effects on pancreatic islet hormone secretion. An evaluation in male volunteers using isoproterenol infusion concluded that it was likely that β -agonist directly activated insulin secretion, but that it perhaps only indirectly activated glucagon secretion.³ More recent studies that used terbutaline in healthy pregnant women at 30 to 34 weeks' gestation confirmed a trend toward both insulin secretion and increased basal glucose levels.⁴ This was taken to reflect a β_2 -agonist-induced decrease in insulin sensitivity of about 30%.

Inhaled β -agonists also have effects on blood sugar regulation. In a recent direct comparison, inhaled formoterol and salmeterol both induced statistically significant modest dose-related increases in plasma glucose, in addition to changes in heart rate, diastolic blood pressure, and potassium concentrations,⁵ confirming an earlier study.⁶ In patients with mild-to-moderate asthma, only the highest doses of inhaled formoterol (48-96 μ g) significantly increased blood sugar concentrations.⁷ Although the average increase induced by the maximum dose was modest (2.6 mmol/L), this could be enough of an increase to meet current definitions of impaired fasting glucose concentra-

From the Department of Medicine, University of Chicago, Chicago, Ill.
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Reprint requests: L. H. Philipson, MD, PhD, Department of Medicine, University of Chicago, 5841 S Maryland Ave, Chicago, IL 60637; E-mail: l-philipson@uchicago.edu.

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tions or even diabetes (126 mg/dL or 7 mmol/L). In patients also receiving steroids, with concomitant weight gain, inactivity, and resulting insulin resistance, the additive effects of β_2 -agonists on blood sugar dysregulation could be difficult to appreciate but still be significant.

These studies suggest that clinically relevant acute doses of either oral, infused, or inhaled β_2 -agonists can result in detectable increases in blood sugar. Additional studies are needed to determine if there is eventual compensation for these effects, perhaps because of potential positive effects on the pancreatic β -cell, as discussed in the next section.

β -agonist effects on regulation of insulin secretion

It has been established that β -agonists and β ARs have a role in insulin secretion from the pancreatic β cell. Before turning to this research, however, a discussion of the fundamental physiologic role of pancreatic β cells will be useful.

Located within the cortex of islets, β cells monitor and respond to moment-to-moment changes in blood glucose concentrations. Under physiologic conditions, secretion of insulin is tightly regulated and is Ca^{2+} -dependent. Glucose-stimulated insulin secretion is regulated by signals produced by glucose metabolism that affect plasma membrane potential and intracellular calcium ($[\text{Ca}^{2+}]_i$). Studies in animals and humans have demonstrated oscillations in plasma insulin concentrations; the normal oscillatory pattern of insulin secretion is perturbed in individuals with diabetes.⁸ These observations suggest the existence of integrated mechanisms that precisely regulate insulin secretion at the level of the pancreas. Many aspects of the mechanisms controlling insulin secretion have been studied in insulin-secreting cell lines, intact islets of Langerhans, and primary β cells in vitro.

Glucose-dependent signal transduction begins with the uptake of glucose into β cells by glucose transporter 2 (Fig 1). Glucose is rapidly phosphorylated by glucokinase and converted to pyruvate in the cytosol by the glycolytic pathway. Pyruvate is oxidized within the mitochondria through the tricarboxylic acid cycle, and adenosine triphosphate (ATP) is generated by oxidative phosphorylation pathways. Glucose catabolism generates ATP that inactivates ATP-sensitive potassium (K_{ATP}) channels. The resting membrane potential of β cells is controlled by K_{ATP} ; closing these channels by an ATP-dependent mechanism initiates plasma membrane depolarization. As the β -cell plasma membrane depolarizes, voltage-dependent Ca^{2+} channels open, facilitating Ca^{2+} influx and Ca^{2+} release from cytosolic Ca^{2+} stores and thereby increasing β -cell $[\text{Ca}^{2+}]_i$. The rise in calcium is part of the stimulus for insulin granule exocytosis, involving a complex interaction of granule proteins and kinases to facilitate docking at appropriate sites in the present membrane, followed by membrane fusion, release of insulin granules, and eventually recycling of the granule membranes.

The insulin secretory mechanism is regulated by numerous receptors, channels, and pumps in the β -cell

membrane. In addition, a gap junctional network coordinates β -cell function throughout the islet. Coordination and regulation is also achieved through autocrine and paracrine actions of other mediators secreted by non β cells and neurons of the islet.

An important aspect of the regulation of insulin secretion is adrenergic tone. The role of β -agonists and β ARs in insulin secretion has been studied for more than 30 years.⁹⁻¹¹ Reduction of insulin secretion follows α AR activation, and increased insulin secretion follows β_2 AR activation. Human β cells express functional β_2 ARs, whereas rat β cells do not seem to respond to β -agonists.¹² In that study, the β_2 -agonist clenbuterol was found to induce a dose-dependent increase in insulin release from human islets incubated in a high concentration of glucose (20 mmol/L), but it had no effect at fasting serum concentrations (4 mmol/L glucose). The clenbuterol-stimulated increase in insulin secretion was inhibited by propranolol. A similar enhancement of glucose-induced insulin secretion in human islets was elicited by salbutamol. In contrast, isolated rat islets were unresponsive to β_2 -agonists.¹² This difference between species has not been closely examined in other studies. The stimulation of insulin secretion by β_2 -agonists is glucose dependent, as seen with several other potentiators of insulin secretion.

The mediators of β_2 -agonist effects in β cells have not been studied in detail. The effects are probably mediated through increasing cyclic adenosine monophosphate (cAMP) concentrations, but additional effects on L-type Ca^{2+} channels, K^+ channels, $[\text{Ca}^{2+}]_i$ stores, and gap junctions are also interesting to consider. A similar set of mechanisms for β_2 -agonist activation of glucagon secretion has been suggested, but the studies of the effect of β -agonist on the islet α cell are contradictory: some find a prompt and specific effect on glucagon secretion and others do not.

Recent studies of the growth-promoting and apoptotic effects of β -agonists, mediated in part by Akt (protein kinase B), suggest that a similar beneficial response might be found in pancreatic β cells.^{13,14} The effects of β_2 -agonists on insulin secretion strongly suggest that further studies are warranted.

β -agonist effects on liver metabolism

Glycogen metabolism plays a critical role in the regulation of blood sugar and the defense against hypoglycemia. The primary mediator of glycogen regulation is through epinephrine and the β ARs,¹⁵ and direct effects on the β ARs and indirect effects on hepatic metabolism by β -agonist induced glucagon release have been suggested. β -agonists also lead to glycogen breakdown and acceleration of glycolysis, in turn leading to impaired glucose tolerance. Liver (and muscle) production of glucose is dysregulated in diabetes.¹⁶ The increased rate of glucose production in type 2 diabetes mellitus has been attributed entirely to increased rates of hepatic gluconeogenesis.

Hepatic effects of β -agonists beyond glycogen regulation have been described. Stimulation of the cAMP-signaling pathway modulates apoptosis in cultured rat hepatocytes.¹⁷ C57BL/6 mice, which have low hepatic β_2 AR densities,

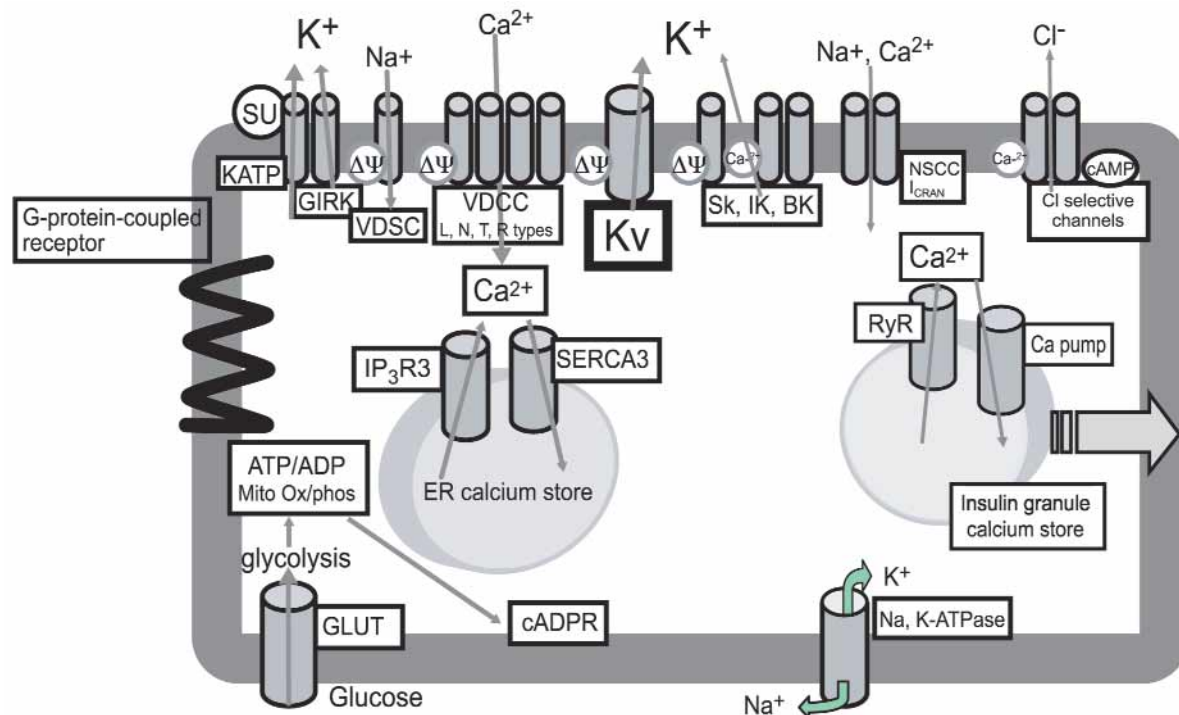


FIG 1. The metabolic model of β -cell function. Under conditions of elevated glucose levels, an increase in the adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio induces closure of K_{ATP} channels. A depolarization results, activating L-type Ca^{2+} channels and leading to elevated $[Ca^{2+}]_i$. Activation of a K^+ conductance, K_v , contributes to the oscillatory pattern of electrical activity and insulin secretion. $cADPR$, Cyclic ADP-ribose; $\Delta\psi$, transmembrane potential; ER , endoplasmic reticulum; $GIRK$, G-protein-gated inwardly rectifying K^+ channels; $GLUT$, glucose transporter 2; IP_3R3 , inositol 1,4,5-triphosphate receptor 3; $NSCC$, Ca^{2+} -release activated nonselective cation current; RyR , ryanodine receptor; $SERCA3$, sarco/endoplasmic reticulum Ca^{2+} adenosinetriphosphatase 3; $Sk/IK/BK$, small/intermediate/large K^+ conductance channels; SU , sulfonylurea receptor-ATP-dependent K^+ channel; $VDCC$, voltage-dependent Ca^{2+} channel; $VDSC$, voltage-dependent sodium channel.

were compared with transgenic F28 mice, which overexpress β_2 ARs and have elevated basal liver adenylyl cyclase activity. The F28 mice were resistant to Jo2, an anti-Fas monoclonal antibody that normally induces liver apoptosis and death. In normal mice, clenbuterol and salbutamol reduced liver apoptosis and death, and propranolol blocked the protective effects. This indicates that the expression level of functional β_2 ARs modulates Fas-regulated liver apoptosis and that this pathway can be inhibited *in vivo* by giving β_2 -agonists.¹⁷ More broadly, this kind of effect suggests a possible therapeutic role for β_2 -agonists in autoimmune disease, such as type 1 diabetes, or a possible adjunctive role in transplant immunosuppression.

β -agonist effects on muscle glucose transport metabolism

Few studies have directly addressed the role of β -agonists in glucose transport. Human studies have shown that muscle glucose transport is inhibited in type 2 diabetes.¹⁶ Two studies in a rat model of obesity and diabetes suggest that β_2 -agonists improve muscle glucose transport. After chronic administration of clenbuterol, leg muscle weights increased and abdominal fat weight decreased, together decreasing insulin resistance in these animals.^{18,19}

The effects of β_2 -agonists on glucose homeostasis are complex. The stimulating effects on glucose production by the liver may be offset by the increased production of insulin and the increased uptake of glucose in muscle and possibly also in fat. Most studies of human subjects involve acute administration of β -agonists, whereas animal studies tend to be long-term and usually involve oral administration of β -agonists. Longitudinal human studies would help to evaluate whether the effects of β -agonists on metabolism are clinically relevant in the long term.

ROLE OF HYPOGLYCEMIA IN β -AGONIST SENSITIVITY

Hypoglycemia is a major problem in the therapy of diabetes mellitus. A very brief discussion will illustrate the connection between hypoglycemia and β -agonists. On one hand, therapeutic choices in diabetes mellitus depend to a great extent on efficacy, with the goal of obtaining as normal a glycohemoglobin level as possible. On the other hand, an increase in the incidence of hypoglycemia with increasingly intensive efforts to improve glycohemoglobin levels has been well documented. One recent study found that the incidence of hypoglycemia

increased by approximately 24% per year from 1993 through 1997.²⁰ Frequent glucose monitoring and intensive insulin administration are associated with frequent recurrent hypoglycemic episodes,²¹ and hypoglycemia thus tends to be the limiting factor in treatment of diabetes. Hypoglycemia itself leads to unawareness of low blood sugars, but detailed studies of this problem and approaches to address it have been developed.²²

In the responses to low blood sugar, stimulation of glucagon secretion is among the most important counter-regulatory mechanisms. It initiates glycogenolysis and gluconeogenesis in the liver through cAMP. Epinephrine is released from the adrenal medulla, triggered in normal persons at ~56 mg/dL, resulting in classic adrenergic symptoms of hypoglycemia: shakiness, trembling, nervousness, tachycardia, and sweating.

In chronic diabetes mellitus, acute glucagon responses to hypoglycemia become defective. Epinephrine is then the critical counterregulatory factor, although the basal level of glucagon in type 1 diabetes is often normal or elevated. Other counterregulatory hormones, cortisol and growth hormone, are not relevant in acute episodes. Lack of awareness of frequent, severe hypoglycemia has become one of the key points for patients being considered for pancreatic islet transplantation.²³ The hypoglycemia unawareness syndrome is caused by the combination of defective responses, primarily involving glucagon and epinephrine.²⁴ Even brief biweekly hypoglycemic episodes can reduce the detection of hypoglycemic episodes.²⁵

Rigorous avoidance of hypoglycemia can reverse the lack of symptoms.²² This may include restored epinephrine secretion, but the primary focus has been on improving the sympathetic response, primarily by improving β -adrenergic sensitivity.²⁶⁻²⁹ In these studies, the β AR sensitivity has been shown to improve after avoidance of hypoglycemia for several months. In one case it improved after removal of an insulinoma, as shown by improved response to isoproterenol 34 weeks after removal of the tumor, which was accompanied by an improved response to hypoglycemia and an earlier release of counterregulatory hormones.²⁷

β -agonists have been suggested as a means to avoid nocturnal hypoglycemia in insulin-treated type 1 diabetes.³⁰ Oral terbutaline was found to be more effective than the conventional bedtime snack in reducing the incidence and severity of hypoglycemia.

Alcohol is a common culprit in hypoglycemia, because it inhibits hepatic glucose production in a way similar to insulin. This can occur many hours after consumption. Alcohol has also been shown to affect the responses to agonist-stimulated adenylate cyclase activity in a variety of cell systems at physiologically relevant concentrations.³¹ Ethanol ingestion may therefore exacerbate a hypoglycemic episode by its effect on hepatic glucose production, diminish the detection of the adrenergic responses, and decrease the ability of the liver to respond to β -adrenergic stimulation.

It is tempting to speculate that persons with the most pronounced difficulties with hypoglycemic unawareness

may be those with β AR polymorphisms.³² Certain polymorphisms can alter the sensitivity of patients to treatment with β -agonists, changing the pharmacodynamics of drug response.³³ The possibilities have been well appreciated in hypertension, asthma, and heart failure.³⁴⁻³⁶ It may be that persons with intensively treated diabetes who have the most severe hypoglycemia reactions and unawareness of hypoglycemia may also have a polymorphism that affects β AR responsiveness and/or desensitization.

β -AGONISTS AND THE ADIPOCYTE

Adrenergic agents have long been known to exert important effects on adipocyte metabolism. Although a detailed discussion is outside the scope of this review, a great deal of evidence points to a critical role of β_3 ARs on the adipocyte.³⁷ For example, recent findings suggest that the β_3 AR plays a central role in regulating the release of leptin from the adipocyte.¹⁵ Leptin release is inhibited by norepinephrine and the selective β_3 -agonist CL316,243. The Trp64Arg mutation of the β_3 AR has been related to the insulin resistance syndrome, an early onset of diabetes, and rapid weight gain.³⁸⁻⁴⁰ Decreased acute insulin release and lower glucose effectiveness in the Trp64Arg genotype may help explain the earlier onset of type 2 diabetes mellitus observed in several populations of persons with this variant allele. However, difficulties in comparing rodent and human data, lack of complete specificity of agonists, and some further complexities introduced by the study of β_3 AR-null mice have made interpretation of studies in this area complex.⁴¹

CONCLUSIONS

β -agonists can affect glucose homeostasis through modulation of insulin secretion, glucagon secretion, hepatic glucose production, and uptake of glucose into muscle. In practice, the effects are detectable but seem to be of little clinical import, unless the patient is on the edge of glucose intolerance. Hypoglycemia can affect β -agonist sensitivity and, conversely, β -agonists may play a role in the treatment or prevention of hypoglycemia. Polymorphisms of the β_3 AR may play a role in the insulin-resistant metabolic syndrome in some populations, and the role of polymorphisms in recurrent hypoglycemia and hypoglycemic unawareness should be seriously considered.

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DISCUSSION SESSION

Question: With hypoglycemia and β -receptor desensitization in patients who are also taking corticosteroids, does this translate into glucose intolerance as measured by hemoglobin A1c? Is this a true confounding factor?

Dr Philipson: This has not really been studied very much. Inhaled glucocorticoids tend not to have a major effect on blood sugar in general. However, in combination with inhaled β_2 -agonists and with other aspects that could cause an increase in insulin resis-

tance, it is possible. It would also be interesting to assess response to the various drugs and study how these drugs work in people who have type 1 diabetes and asthma.

Question: The suggestion that maybe episodes of increased circulating catecholamines lead to catecholamine nonrecognition during hypoglycemia episodes suggests the possibility of heterologous desensitization at a very different level. What about exercise-induced increases in circulating catecholamines? Is exercise bad for diabetics?

Dr Philipson: No, exercise is good. However, remember, exercise has a completely independent effect on glucose uptake. So, there is insulin-independent glucose uptake in muscle, which would be countervailing there. What you want is improved insulin sensitivity, decreased insulin production, and improved glucose uptake. So exercise is in fact what would work.

Question: What about receptor polymorphisms in the people who are unaware of hypoglycemia?

Dr Philipson: I think this needs to be studied. It may be unrelated, but it is interesting that hypoglycemic unawareness is the critical problem in intensive management of type 1 diabetes. It is the number-one criterion that propels patients to the top of the list in any islet or pancreas transplant program.

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