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# Glucagon orchestrates stress-induced hyperglycaemia

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Hyperglycaemia is commonly observed on admission and during hospitalization for medical illness, traumatic injury, burn and surgical intervention. This transient hyperglycaemia is referred to as stress-induced hyperglycaemia (SIH) and frequently occurs in individuals without a history of diabetes. SIH has many of the same underlying hormonal disturbances as diabetes mellitus, specifically absolute or relative insulin deficiency and glucagon excess. SIH has the added features of elevated blood levels of catecholamines and cortisol, which are not typically present in people with diabetes who are not acutely ill. The seriousness of SIH is highlighted by its greater morbidity and mortality rates compared with those of hospitalized patients with normal glucose levels, and this increased risk is particularly high in those without pre-existing diabetes. Insulin is the treatment standard for SIH, but new therapies that reduce glucose variability and hypoglycaemia are desired. In the present review, we focus on the key role of glucagon in SIH and discuss the potential use of glucagon receptor blockers and glucagon-like peptide-1 receptor agonists in SIH to achieve target glucose control.

**Keywords:** critical illness, glucagon, ICU, insulin, stress-induced hyperglycaemia

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## Introduction

Under normal physiological conditions, glucagon produced in the $\alpha$ cells of the pancreas acts primarily on the liver to increase hepatic glucose output to maintain an adequate supply of fuel to the brain and other vital organs [1,2]. In uncontrolled type 1 diabetes mellitus (T1D) and type 2 diabetes mellitus (T2D), hyperglucagonaemia is universally present, suggesting aberrant glucagon secretion [3–5]. Several lines of evidence indicate that the hyperglucagonaemia of diabetes is the direct result of loss of insulin-induced suppression of pancreatic $\alpha$-cell glucagon secretion [6–8]. Glucagon-induced hepatic glucose output has been implicated as a major cause of uncontrolled diabetes. In subjects with T1D, suppression of glucagon secretion by somatostatin without changing insulin levels ameliorates hyperglycaemia [9,10]. In patients with T2D, glucagon receptor blockers decrease fasting and postprandial glucose [11–13]. Preclinical studies in glucagon receptor knockout mice have demonstrated protection from diabetes after complete $\beta$-cell destruction, providing support for the hypothesis that excess glucagon secretion is directly responsible for many of the metabolic perturbations of diabetes [14–16].

Relative insulin deficiency, insulin resistance and concomitant increases in the counter-regulatory hormones (i.e. glucagon, epinephrine and cortisol) are present in medically ill patients with hyperglycaemia and, under experimental conditions, administration of this hormonal cocktail to normal healthy subjects produces metabolic changes resembling stress-induced hyperglycaemia (SIH) [17–21]. Although the individual effects of insulin, glucagon, cortisol and epinephrine on normal glucose metabolism are well described, the contribution of each to metabolic changes in the setting of medical illness is more difficult to define. In this review, we will focus on what is known about hyperglucagonaemia in the context of the complex hormonal milieu of SIH. We will also discuss the potential for glucagon receptor blockers and glucagon-like peptide-1 (GLP-1) receptor agonists to treat SIH, with the goal of causing less glucose variability and hypoglycaemia than with insulin, the standard of care.

## Stress-induced Hyperglycaemia

Stress-induced hyperglycaemia, also referred to as stress hyperglycaemia, hospital hyperglycaemia or hyperglycaemia of critical illness is a serious and common condition where blood glucose levels >140 mg/dl occur during hospitalization for traumatic injury, burn, surgery and critical or acute medical illness [22–29]. SIH typically resolves on recovery from the acute medical insult and before discharge from the hospital. Some restrict the use of the term SIH to those patients without a history of diabetes, while others include all patients irrespective of their baseline diabetes status. In the present review, patients previously diagnosed with diabetes and those with no medical history of diabetes will be discussed together. SIH typically occurs in 35–40% of all hospitalized patients when 140 mg/dl is used as the threshold [23]. In a more recent study assessing almost 50 million point-of-care glucose values from over 3.4 million patients, the prevalence of hyperglycaemia (>180 mg/dl) was 32.2% in patients in intensive care units (ICUs) and 32.0% in non-ICU patients [30]. Approximately 70–80% of patients with SIH admitted to the ICU have no

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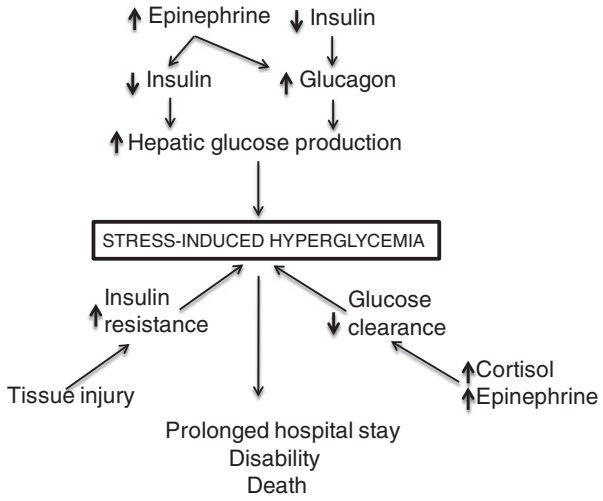


**Figure 1.** Diagram of hormonal mechanisms of stress-induced hyperglycaemia.

history of diabetes [23,31]. With over 38 million US hospital discharges per year in 2011 and the high prevalence of SIH, this condition is estimated to affect millions annually and has a substantial impact on healthcare costs [32–34].

Glucose levels that are well above normal are believed to be maladaptive in SIH and exert an array of negative effects, primarily through immune dysfunction and oxidative stress [35–38]. These adverse effects contribute to the morbidity and mortality associated with SIH, where substantial increases in infections, need for kidney dialysis, blood transfusions, polyneuropathy and up to an 18-fold increased risk of death have been described [23,25,26,39,40].

The underlying cause of SIH is thought to be a combination of insufficient insulin secretion to overcome the hyperglycaemic effects of counter-regulatory hormones and insulin resistance in the later stage of illnesses that have significant amounts of tissue injury (Figure 1) [21,41–43]. One study, designed to determine the effect of trauma on insulin secretion, used graded glucose infusions to induce hyperglycaemia and found that insulin secretion was impaired in patients with major and minor trauma compared with normal individuals [44]. In subjects with major trauma, the impairment in insulin secretion persisted for at least 5 days, while insulin secretion returned to normal sooner in patients with minor trauma. Other studies have shown decreased insulin secretion during the shock phase of burns [19] or in the early hours after myocardial infarction [17]. Taken together, these data indicate that diminished insulin secretion during the early phase of multiple types of illnesses and injuries is a key contributor to the onset and persistence of SIH. In contrast, insulin resistance appears more prominently during the established or recovery phase of SIH, particularly in situations of severe tissue injury [19].

Studies in lean and obese healthy human volunteers have advanced the concept that simultaneous intravenous infusion of glucagon, epinephrine and cortisol, without the addition of exogenous insulin or experimental alteration in insulin secretion is sufficient to replicate the metabolic effects of SIH [21,45,46]. Insulin secretion is typically reduced relative to the level of hyperglycaemia and is not able to compensate for the combined effects of the counter-regulatory hormones [17,19,44]. Additional neuro-hormonal factors and cytokines may play a modulatory or secondary role in SIH [47–50].

Treatment of patients with SIH is limited primarily to insulin administration, irrespective of diabetes status and baseline pancreatic $\beta$-cell reserves. In critically ill ICU patients, intravenous insulin infusion is typically used, while basal and supplemental subcutaneous insulin is preferred in those who are not critically ill. Most current treatment guidelines recommend maintaining glucose in the 140–180 mg/dl range for patients in the ICU [22,51,52]. A pivotal single-site study demonstrated in critically ill patients that intensive insulin therapy to reduce glucose to a target range of 80–110 mg/dl improved outcome and decreased length of ICU and hospital stay [39]. Tight glycaemic control was then reported to translate into significant healthcare costs savings [29,53,54]. However, a subsequent large multicentre trial determined that a glucose target of <180 mg/dl resulted in lower mortality than glucose targets of 81–108 mg/dl. This landmark study moved the standard of care away from tight glycaemic control with intensive insulin therapy in critically ill patients [55].

The prevalence of insulin-induced hypoglycaemia in SIH clinical trials can exceed 6%, even when more conservative glucose levels are targeted [56,57]. Of greater concern is that in clinical practice, hypoglycaemia rates have been reported of up to 20% in ICU patients with SIH [58]. When hypoglycaemia is severe it can cause death from cardiovascular or neural events [56].

In addition to targeting mean glucose levels and avoiding hypoglycaemia, glucose variability has emerged as a key variable in predicting outcome in critically ill patients. One retrospective observational study of >7000 patients in four ICUs in Australia determined that glucose variability measured by the blood gas analyser and targeting glucose values of 6 and 10 mM, with no specific insulin protocol, was a significant and independent predictor of ICU and hospital mortality [59]. Glucose variability was a stronger predictor of ICU mortality than mean glucose concentration. In that study, ICU mortality was 12% and hospital mortality 22%. Studies in other ICU populations have corroborated these results [60,61]. More recent studies have determined that glucose variability is a stronger predictor of mortality in ICU patients without a history of diabetes compared with those with a history of diabetes [62].

Lastly, insulin administration requires a significant amount of the healthcare provider's time to adjust the insulin dose to achieve target glucose control. Although insulin itself is relatively inexpensive, monitoring requirements contribute to the increase in healthcare costs [34,53]. Thus, novel therapies are needed that are easy to administer and are able to achieve optimum glucose control while avoiding hypoglycaemia and glucose variability [63].

## Regulation of Glucagon Secretion in Stress-induced Hyperglycaemia

Elevated blood glucagon levels in relatively young healthy patients with traumatic injuries were described >40 years ago

[64,65]. Soon thereafter, it was discovered that people admitted for a variety of medical illnesses, including acute myocardial infarction [42,66], burns [67,68] and sepsis [41], also had elevated glucagon levels of up to five times the normal level. A common finding across the studies was that the degree of glucagon elevation was positively correlated with the severity of the medical illness. Glucagon levels typically did not return to baseline until the patient had recovered from the illness or injury. These data, along with others, have led to the notion that glucagon is a stress response hormone, potentially with effects beyond glucose homeostasis [69]

Under normal physiological conditions, glucagon secretion from pancreatic $\alpha$ cells is regulated by fluctuations in plasma glucose, either directly or indirectly through the autonomic nervous system, circulating hormones, GLP-1, and secretory products from other islet cells [70]. Factors known to suppress glucagon secretion, including insulin, may be absent or low in medical illness when a patient is often not eating normal amounts of food and when stress levels of catecholamines, which suppress insulin secretion, are very high [6,42,71]. There is evidence that most of the inhibitory effect of insulin on glucagon secretion is mediated by paracrine effects within the pancreatic islets [8,72,73]. Studies in $\alpha$-cell-specific insulin receptor knockout mice have confirmed that insulin decreases glucagon secretion through direct effects on $\alpha$ cells [7]. In hyperinsulinaemic–euglycaemic clamp studies in subjects with T1D, insulin administration to attain blood levels of ~500 μU/ml, lowered plasma glucagon levels by 20–30%, confirming the suppressive effect of insulin on glucagon secretion [6]; however, using supraphysiological insulin levels to suppress glucagon secretion to this degree in hyperglucagonaemic patients with SIH will probably not be sufficient to suppress glucagon to normal levels.

Epinephrine has been shown to directly stimulate glucagon secretion [2,74]. In non-diabetic individuals; epinephrine stimulates glucagon secretion primarily through $\beta$-adrenergic receptors with $\alpha$-adrenergic receptor stimulation, accounting for no more than 20% of the effect [75]. In healthy subjects, epinephrine infusion causes only a modest 19% increase from baseline in glucagon levels [76]. This effect of epinephrine on glucagon levels is relatively small compared with the three-to-fivefold increase in glucagon levels seen in patients with medical illness. Under extreme stress conditions, however, e.g. after cardiac arrest, epinephrine levels can increase 1000-fold from normal levels of <0.05 ng/ml and may thus have a greater effect on glucagon secretion in the critically ill patient [77].

Endogenous cortisol was not found to alter glucagon secretion in healthy volunteers given adrenocorticotropic hormone to stimulate cortisol production [78]. However, earlier studies found that exogenous glucocorticoids given for 3 days increased blood glucagon levels by 55% in non-diabetic lean and 110% in non-diabetic obese individuals [79]. Furthermore, a recent cross-sectional prospective study found that 0.6% (6 out of 813) patients with T2D in diabetes clinics who had no overt hypercortisolism had Cushing's syndrome [80]. The diabetes was cured in four of the six patients after treatment of their Cushing's syndrome and normalization of cortisol.

Other factors may influence glucagon secretion in SIH, but no studies have conclusively identified the dominant inducer of hyperglucagonaemia. The preponderance of evidence suggests that intra-islet insulin deficiency or insulin resistance, epinephrine excess or a combination of these factors, drive most of the excessive glucagon secretion in SIH.

## Novel Treatment Approaches to Stress-induced Hyperglycaemia

*Glucagon-like Peptide-1 Receptor Agonists.* Dysregulated GLP-1 secretion or GLP-1 deficiency is not a well-defined feature of SIH, but ~50% of the glucose-lowering effect of GLP-1 receptor agonists, approved for the treatment of T2D, has been attributed to suppression of glucagon secretion, making this class of agents a plausible treatment option in patients with SIH [81]. There have been several clinical trials of GLP-1 receptor agonists in hospitalized patients admitted to the coronary care unit [82], on total parenteral nutrition [83], and in other situations of critical illness [84]. In general, GLP-1 receptor agonists have been shown to be effective in glucose-lowering, to reduce glycaemic variability [85], and to result in equal or less hypoglycaemia compared with insulin, but with increased nausea and vomiting in the hospital setting. One study in nine patients with hyperglycaemia, receiving total parenteral nutrition infused with GLP-1, showed an ~50-mg/dl glucose-lowering effect, as well as an increase in plasma insulin and C-peptide, and a trend towards a reduction in glucagon and free fatty acids [83]. The glucagon-lowering effects of GLP-1 infusion were also seen in a study of critically ill surgical patients [85]. Patients who have undergone coronary artery bypass grafting, with preserved left ventricular function, who were treated with continuous infusion of a GLP-1 receptor agonist peri-operatively had better glycaemic control with less insulin administration and fewer arrhythmias requiring antiarrhythmic agents compared with a control group [86]. Thus, GLP-1 receptor agonists are potential alternatives to insulin for the treatment of SIH, but nausea and vomiting are potential undesirable effects.

*Glucagon Receptor Antagonism.* As discussed previously in this review, hyperglucagonemia is common in SIH and has the potential to initiate or worsen hyperglycaemia. Thus, glucagon receptor blockers may be a reasonable alternative or adjunct to insulin therapy to treat SIH during the hospital admission. An early study in patients with burns showed that infusion of somatostatin, an inhibitor of glucagon and insulin secretion, for 30 min, significantly reduced the rate of glucose production [87,88]. Somatostatin administration as a therapeutic tool in SIH, however, would require concomitant administration of insulin to counter the suppressive effect on insulin secretion. In addition, somatostatin analogues that are approved to treat other conditions, such as acromegaly, have been shown to cause biliary tract abnormalities including; gallstones, sludge without stones, and biliary duct dilatation in a high percentage of patients [89]. For these reasons, somatostatin analogues are not likely to be treatment options to decrease hyperglucagonemia and control glucose in patients with SIH.

Studies investigating glucagon receptor antagonist for the treatment of SIH have not been reported. Based on clinical trials of small-molecule glucagon receptor antagonists in patients with T2D, these agents may provide an effective alternative to insulin therapy, but with a lower incidence of hypoglycaemia and potentially reduced glucose variability [11,13,90]; however, reversible adverse effects of increased LDL cholesterol and liver enzymes have been reported in early-phase T2D trials with small-molecule glucagon receptor blockers [11,13,90]. Preclinical studies suggest the pharmacokinetic and pharmacodynamic properties of anti-glucagon receptor antibodies may also be an effective approach to treat SIH. One study in diabetic monkeys of a human monoclonal blocking antibody to the glucagon receptor showed that a single dose had a rapid onset of action within hours, with sustained glucose-lowering over a 7-day period [91]. Studies with another antibody in obese hyperglucagonaemic mice showed a decrease in hepatic glucose output, the main culprit of SIH [92]. Future studies will determine whether glucagon receptor antagonists that have a rapid onset of action offer a safe and effective treatment option for SIH.

## Conclusions

Stress-induced hyperglycaemia is a major medical problem requiring prompt treatment of the hyperglycaemia to decrease morbidity and mortality. The complex interplay between relative insulin deficiency in early stages of severe illness, combined with evidence that the elevated levels of glucagon, epinephrine and cortisol sustain hyperglycaemia, suggest that insulin moderates only some of the hormonal dysregulation observed in SIH. Thus, insulin alone may not be an optimum treatment strategy for SIH and may in fact contribute to increased morbidity and mortality by causing hypoglycaemia and increased glucose variability. GLP-1 and GLP-1 receptor agonists approved for the treatment of T2D have shown some promise in hospitalized patients with hyperglycaemia when infused continuously. Given that glucagon receptor blockers are in development for T2D, consideration of these agents for SIH deserves exploration in future clinical trials as they may address the hyperglycaemia, while resulting in less glucose variability and insignificant hypoglycaemia, and requiring less intensive glucose monitoring. It remains to be seen whether the transient increase in liver enzymes and other adverse effects will stall further development of this class of agents.

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