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Continuous Glucose Monitoring Functions as a Negative Feedback Loop for Individuals with Type 2 Diabetes

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ABSTRACT

To maintain homeostasis, the body employs negative feedback loops that track the current state of a system and trigger regulatory responses when certain thresholds are exceeded. Monitoring current status typically employs processes that trigger either endogenous or exogenous regulatory responses, such as low blood pressure triggering heart rate acceleration or hunger triggering eating. In the case of diabetes, euglycemia is achieved by glucose feedback directing self-regulatory behaviors. Continuous glucose monitoring (CGM) can uniquely provide accurate, precise, immediate and relevant exogenous feedback to activate, educate, motivate and investigate optimal self-regulatory behaviors by individuals with type 2 diabetes.

INTRODUCTION

Negative feedback occurs when the output of a system, process, or mechanism is returned towards its initial status. This reduces subsequent fluctuations in the output, whether caused by changes in the input or by other disturbances [1]. Negative feedback loops are central in behavioral, economic, engineering and biological systems. They aim to maintain the normal system status, or achieve homeostasis, by decreasing output variability. A high degree of variability characterizes failing systems. Functional negative feedback loops require accurate, timely and relevant information concerning the current state of the system and provide an efficient and effective corrective mechanism.

In biology, negative feedback loops are pervasive throughout the body. They maintain relatively narrow operating ranges for physiological processes like body temperature, blood oxygen levels, and digestion. For example, the baroreceptor reflex, or baroreflex, is one of the body's homeostatic mechanisms that helps one maintain blood pressure at nearly constant levels. The baroreflex is part of a rapid negative feedback loop in which elevated blood pressure reflexively causes heart rate and blood pressure to decrease. Conversely, lower blood pressure decreases activation of the baroreflex which causes heart rate to increase, restoring blood pressure levels. The baroreflex can begin to act in less than one cardiac cycle, thus baroreflex feedback is a key factor in dealing with postural hypotension. This system relies on specialized neurons known as baroreceptors, found in the aortic arch, carotid sinuses and elsewhere, to monitor changes in blood pressure and relay the information

to the medulla. Baroreceptors are active at normal blood pressure levels so that their activity can inform the brain about increases and decreases in blood pressure [2].

A simple description of the normal physiology of Blood glucose (BG) control is that peripheral sensors in the liver and portal vein (among others) and central sensors in the brain detect blood glucose levels above about 100mg/dl and activate pancreatic beta cells to release the regulatory hormone, insulin. This promotes glucose utilization in cells throughout the body and storage of excess glucose in skeletal muscles, adipose tissue and the liver. When sensors in brain areas such as the ventromedial hypothalamus detect that blood glucose has fallen below about 80 mg/dl, pancreatic alpha cells are activated to release the counter-regulatory hormone, glucagon. This triggers glycogenolysis in the liver, which results in the release of stored glucose. This limits glucose uptake in the liver and promotes gluconeogenesis (i.e. the production of glucose from 3-carbon amino acid and fatty acid molecules such as alanine, lactate and glycerol).

Homeostasis goes awry when either the feedback or the response becomes dysfunctional. In the case of type 2 diabetes (t2d), the automated feedback from high BG that triggers the regulatory response of insulin secretion is less than needed. It is also less effective because insulin resistance makes the regulatory response ineffectual. Thus, BG remains high, triggering more insulin release, and hyperinsulinemia can result. The conventional treatment of regulatory hormone dysfunction is to reduce insulin resistance, either by altering lifestyle (through weight loss or exercise) or by using pharmacological interventions to reduce insulin resistance, reduce glycogenolysis and gluconeogenesis, or increase insulin release.

The body often relies on external, self-regulating behaviors to maintain internal homeostasis. For example, pain may trigger the exogenous response to cease placing pressure on a wound, or the feedback of hunger might trigger nutrient intake. However, modest swings in BG are typically asymptomatic, so exogenous feedback is required to activate corrective self-regulating behaviors. Hippocrates achieved this by tasting sweetness in the urine. Subsequently this was measured with urine strips. However, the feedback provided by both of these methods is too slow and lacks precision. Self-monitoring of blood glucose (SMBG) provides immediate, precise and relevant information about BG, but by itself, it is ineffective in improving BG control in t2d [3]. This may be because it is done too infrequently and not systematically making it hard to interpret and act on. SMBG cannot tell you when and how quickly BG is rising into hyperglycemia or falling into hypoglycemia. Therefore, because it cannot signal BG dynamics SMBG cannot trigger timely corrective behaviors to reverse high or low BG.SMBG suffers from other significant limitations: It can be uncomfortable, expensive, and inconvenient. It requires available opportunity and equipment, and it gives a static reading that does not indicate the speed or direction of BG change.

Continuous glucose monitoring circumvents many of these feedback limitations. Once activated, it provides feedback about both the direction and speed of BG change. It tells one where their glucose has been, where it is now, and whether it is changing slowly or quickly, it can alert when thresholds are exceeded. It does this immediately, accurately, conveniently and clearly [4,5]. All of these are critical elements of an effective negative feedback loop to direct self-regulatory behaviors.

CGM has at least four qualities that make it an especially effective biofeedback device for self-regulation of t2d: 1) It can ***activate*** self-regulatory behavior. Alerts to high glucose can initiate glucose lowering behaviors (e.g., exercise) and alerts to low glucose can start glucose raising behaviors (e.g. consuming carbohydrates). 2) CGM feedback can ***educate*** individuals about their glucose regulating system. Individuals can learn how much their glucose increases with different foods and amounts of these foods, as well as how much their glucose decreases with different types and durations of physical activity. 3) CGM feedback can ***motivate*** individuals to repeat nutrient and activity choices that led to desirable glucose levels and discourage them from repeating choices that resulted in undesirable glucose consequences. 4) CGM can encourage individual's to ***investigate*** personal glucose disruptions. For example, CGM could alert an individual to spontaneous morning glucose elevations and assist them in determining whether subsequent actions, such as time-limited eating [6], reduce their morning glucose elevations.

It is important to note that in the management of type 1 diabetes, CGM typically performs a different role: It prompts

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the immediate increase or decrease of insulin dosing or prompts the ingestion of rapid-acting carbohydrates with pending hypoglycemia. The analysis of temporal patterns of glucose levels is also a possible benefit of CGM in the management of type 1 diabetes. This is different from its possible use with t2d when they do not take insulin, which focuses more exclusively on providing BG feedback that promotes education, motivation and investigation regarding glucose management.

In a recent pilot study [7], we demonstrated the utility of CGM for achieving these ends in people with t2d.We are currently conducting a clinical trial that compares the effectiveness of CGM, systematic SMBG, and routine care for those with t2d.Until these results become available, we encourage researchers and clinicians to consider the possibility of using CGM with t2d as a negative feedback loop in research and patient care to optimize self-regulatory behaviors.

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