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Pharmacological aspects of closed loop insulin delivery for type 1 diabetes

Chukwuma Uduku and Nick Oliver

Insulin deficiency and impaired glucose homeostasis are hallmarks of type 1 diabetes. Since the discovery of insulin, pharmacological and clinical developments have endeavoured to replicate its endogenous pharmacokinetics (PK) and pharmacodynamics (PD). Closed loop insulin delivery systems operate as an artificial pancreas by making automated insulin dose adjustments based on real time continuous glucose monitoring. The increasing adoption of continuous insulin pump therapy and evolving technological advances have seen significant progress in the development of closed loop insulin delivery systems. This article reviews the current landscape of closed loop insulin delivery systems and pharmacological advances that could overcome current barriers.

Address
Division of Diabetes, Endocrinology and Metabolism, Faculty of Medicine, Imperial College, London, UK

Corresponding author: Oliver, Nick (nick.oliver@imperial.ac.uk)

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Introduction

Type 1 diabetes is characterised by insulin deficiency secondary to the autoimmune destruction of pancreatic beta cells. Intensive glycaemic control with insulin therapy can reduce the incidence of microvascular and macrovascular disease in type 1 diabetes independently of other modifiable risk factors. However, this is associated with an increased hypoglycaemia risk [1–3]. The enduring goal in diabetes care is to develop a safe mode of insulin delivery that mimics physiology and optimises HbA1c, a measure of overall glycaemia, without associated hypoglycaemia.

At present, the most accessible mode of insulin replacement remains subcutaneous (sc) multiple daily injections or continuous subcutaneous insulin infusion (CSII) via a pump. Despite developments in both treatment modalities, postprandial glucose excursions and hypoglycaemia remain an ongoing obstacle. The increasing adoption of CSII and the integration of continuous glucose monitoring (CGM) alongside insulin pump technology has paved the way for closed loop insulin delivery and artificial pancreas system (AP) development. A closed loop insulin delivery system consists of an insulin pump, a CGM and a glucose control algorithm. Glucose control algorithms are a set of programmed rules which allow the glucose controller to perform the role of a normal pancreas and make automated insulin adjustments based on real-time CGM data [4] (Figure 1).

The control algorithm can be integrated in the insulin pump or the control function may be incorporated into a dedicated mobile device or smart device app that communicates wirelessly with both CGM and insulin pump. The interaction between these components is the cornerstone of AP systems in contrast to conventional CSII therapy where the user is required to interpret blood glucose values and adjust insulin doses.

The strategy to control glycaemia can vary from focusing solely on preventing hypoglycaemia and extreme hyperglycaemia to more complex systems that maintain euglycaemia within a target range (treat to range) or to a specific value (treat to target) [5–8]. At present, the two most widely used control algorithms in AP development are Model Predictive Control (MPC) and Proportional Integral Derivative (PID). PID is a reactive control algorithm that responds to deviations from target glucose levels and the rate of glucose level change. MPC proactively anticipates future glucose levels on the basis of current concentrations. The first head to head randomised crossover trial comparing PID and MPC in an AP system demonstrated safe glycaemic control using both control algorithms. However, MPC significantly demonstrated more time within target glycaemic range, and lower mean glucose overall and 5 hours after an unannounced 65 g meal [9•].

CGM is an integral component of a closed loop insulin system directly influencing the control algorithm and real-time insulin dose adjustment. CGM devices measure changes in glucose concentration in the interstitial fluid through a sensor deployed in the sc tissue. Signals from the sensor are processed to display an estimated glucose level via a wired or wireless connected display. Glucose estimations are made using an enzyme linked to an electrode producing currents that are directly proportional to glucose levels. Although interstitial glucose

Figure 1

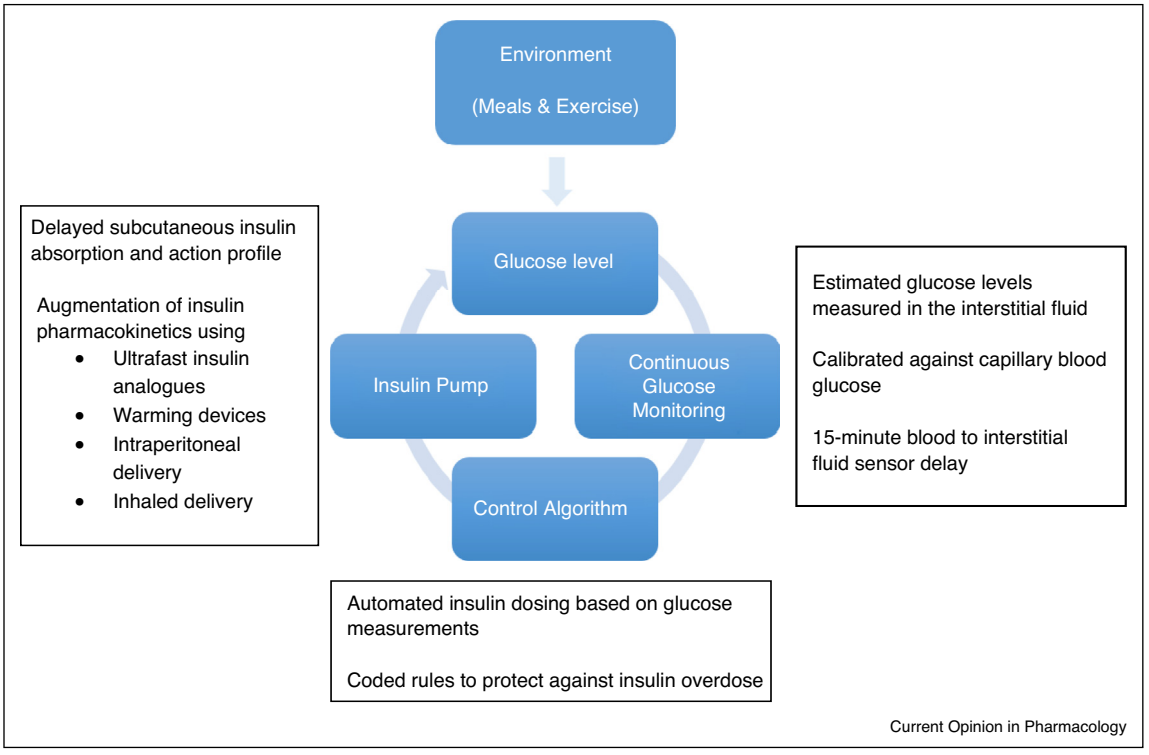

Illustration of a closed loop automated artificial pancreas system.

levels accurately represent trends in blood glucose concentration, there remains a sensor lag of up to 15 min between peak blood glucose and interstitial fluid levels [10]. This highlights the need for capillary glucose measurement for sensor data calibration during periods of stable glucose control in AP systems.

The risk of hypoglycaemia for people with type 1 diabetes has reduced over time with the introduction of analogue insulins, improvements in education, and adoption of technologies including CGM and CSII [11,12]. Anticipating and responding to external factors that rapidly alter glycaemia such as meals and exercise remains a major challenge when designing closed loop systems. Most pump devices incorporate bolus calculators accounting for circulating insulin on board which have achieved significant reductions in average glucose and overnight glucose variability without increased hypoglycaemia risk [13]. The PK and PD of sc insulin also create obstacles when developing AP systems. The non-physiological kinetic profile and biological distribution of sc insulin results in delayed absorption and loss of the positive portal to peripheral insulin gradient observed physiologically. This imbalance is believed to diminish first phase hepatic insulin activity and the ability to control postprandial glycaemia by regulating hepatic glucose output. Further challenges to AP systems arise from real world events such as exercise and varied meal times. Despite these obstacles, the development of closed loop systems has moved from *in silico* testing to clinical assessment during free-living home conditions. Randomised crossover studies comparing closed loop AP insulin delivery with sensor-augmented pump therapy in home settings successfully showed significantly improved glycaemic control, reduced hypoglycaemia and lower Hba1c [14,15]. Such promising data and FDA approval for the first hybrid closed loop system in September 2016 are steps towards the introduction of closed-loop systems in clinical practice. In this review, we will summarise pharmacological aspects, from insulin absorption, site of administration, use of insulin adjuncts and bi-hormonal systems as potential solutions to these obstacles.

Insulin formulation

Rapid acting insulin analogues (RAIs), lispro, aspart and glulisine, are associated with faster insulin exposure, faster peak action and shorter overall duration of action. These factors translate to greater HbA1c reductions and reduced hypoglycaemia risk compared to regular human insulin [16–18]. Nonetheless, the onset of action of RAIs remains slower than endogenously secreted insulin and require an injection to meal time interval of 15–20 min to achieve optimal postprandial glucose control [18,19]. To overcome this delay, a closed loop system ideally requires